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CLINICAL RESEARCH USING COMPOUNDS LABELED WITH RADIOACTIVE CARBON AND HYDROGEN AS TRACERS *

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ISOTOPES can be used in clinical research in two principal ways: first, to simplify existing analytic or diagnostic methods; and second, to study phenomena that cannot be examined readily, if at all, by conventional biochemical methods. There is no really good reason for considering the first option less important than the second, especially if the use of radioisotopes permits one to do more work, or to do it more accurately. It is easy, however, to become fascinated with the technical or electronic aspects of isotopes to the extent that interest in the physiologic problem is subordinated. It is possible to conduct studies with radioisotopes that are probably not worth doing. A simple example will illustrate the point I wish to make. It should be possible to prepare radioactive phenolsulfonphthalein (PSP) and perform clinical tests of kidney function, using the labeled material. The results would be determined with a Geiger counter instead of an old-fashioned comparator block, or a colorimeter. Unless a very large increase in accuracy resulted, or unless it was found to be much simpler technically, there would be no advantage in the substitution of the radioisotopic method, since it could not yield any new information about the kidney that was not obtained by the familiar, less dramatic procedure. In contrast to this, consider the use of radioisotopic methods to measure blood volume. The Evans blue dye method and the I^{131}-labeled human serum albumin method are equally useful for the estimation of plasma volume. The radioisotopic procedure, however, is simpler to perform, can be repeated at more frequent intervals, and is technically more accurate than the blue dye method. Any plasma volume

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From the Department of Medicine and the Argonne Cancer Research Hospital, The University of Chicago.

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method that depends on the tagging of albumin is unreliable in certain classes of patients; for example, those in congestive heart failure. In such conditions other methods of measuring blood volume are preferred. The easiest and most reliable methods for determining the volume of the red cells and the blood volume involve the use of radiochromium or radiophosphorus.

Radioactive isotopes can be valuable analytic tools for the study of the distribution and the fate of therapeutic agents and of toxic chemicals. A good example of this application is the work of Barclay, Ebert et al.[1] with the antituberculosis drug, isonicotinic acid hydrazide (INH). Murray and Langham [2] were able to synthesize INH labeled with C^{14} in the carboxyl group. After preliminary trials in normal and in infected animals, the labeled drug was given to patients with surgical forms of tuberculosis. Since it had been established that the drug was not broken down in vivo, the radiocarbon content of tissue, blood, spinal fluid and pleural fluid was equivalent to the concentration of INH. The amounts of INH that are bacteriostatic for susceptible tubercle bacilli are too small to be detected chemically in biological material. However, on the basis of the measurements of radiocarbon, expressed in microgram equivalents, Ebert's group demonstrated therapeutically significant amounts of INH within caseous tubercles, in pleural effusions, in skin and in cerebrospinal fluid. The implications of such a study are obvious.

The outstanding contribution of isotopic methods * to biochemistry has been the development of the concept of the dynamic state of the body's constituents. A corollary of this concept is the appreciation of the fact that a healthy organism is a complex chemical system that is in a steady state, or that is in equilibrium. Under these conditions, the input of food and oxygen is balanced nicely by the output of work and waste products. In spite of variations in the composition of the food, the chemical composition of the body remains remarkably constant while in a state of health. It is appropriate to think of disease as a disturbance of the steady state, as the establishment of a different and less favorable equilibrium, or as the failure to achieve any equilibrium at all, with death as the final result. The terms that describe a system in the steady state are:

1. The volume of the system, and of its components;
2. The concentration of the constituents; and
3. The rate at which input, output and interconversions occur.

By definition, in the steady state, the rate of appearance, synthesis or production of any constituent is equal to the rate of disappearance, utilization or excretion of that substance. It would be very convenient if we could always simplify matters and consider the entire body as a single pool, or compartment, in a steady state (figure 1). In point of fact, this is the concept that we employ when we measure the minute oxygen consumption as an indicator

* Throughout this discussion remarks about isotopes refer to either stable or radioactive forms.

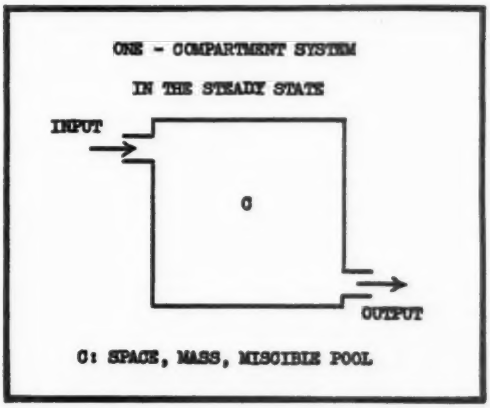

FIG. 1. Simplified diagram of a one-compartment system. At equilibrium input equals output, and concentration should be constant.

of the basal metabolic rate. Unfortunately, it is usually necessary to think of the body as composed of many compartments between which there is a measurable movement of gases, metabolites, electrolytes and waste products (figure 2). The future description of disease might well be a statement of the abnormality in the size of the compartments, of the rate of exchange between them, and of the concentrations and rates of interconversion of substances within the compartments.

Historically, this concept of the living organism is a recent development, and is due almost entirely to the discovery of isotopes. This is necessarily

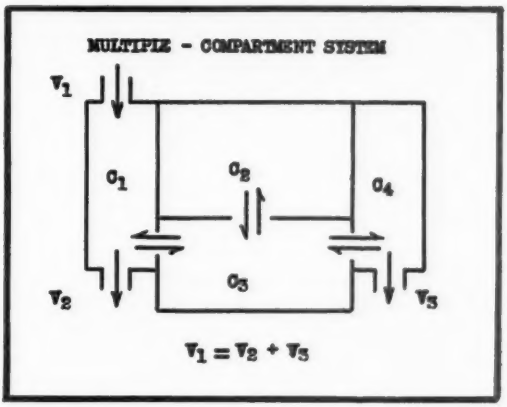

FIG. 2. Simplified diagram of a multiple-compartment system. At equilibrium, the reactions between the various compartments proceed at constant rates, so that the concentration in the compartments is also constant. Ideally, input equals output in this case.

the case, since it was not possible to trace the movements of gases, metabolites or electrolytes until a method for labeling them was available. The first common substance to be used in this way was heavy hydrogen, or deuterium (H^2), which was discovered and made available for biological research by Harold Urey in the 1930's.* The Swedish physiologist, Georg Hevesy, then showed that the body did not distinguish between ordinary water and heavy water, and thus established the fundamental basis for all isotope research in biology and medicine. Since Hevesy's pioneer investigations in 1934, and since the original biochemical studies of Rittenberg and Schoenheimer starting in the same year, there has been a revolution in our understanding of physiologic and biochemical processes. The early work was hampered by the technical difficulties involved in the measurement of the substances labeled with stable isotopes. Since these measurements depend upon small differences in mass, extreme precision is required at every stage of the analysis. The technical problems of isotopic analysis have been greatly simplified by the use of radioisotopes, where one is concerned principally with the problem of precise detection of beta or gamma radiation. At least two biologically important elements, nitrogen and oxygen, do not have useful radioactive isotopes, so that clinical research with them must be performed with their stable isotopes. At the present time, radioactive carbon (C^{14}) has virtually replaced stable carbon (C^{13}) in biologic research, just as radioactive tritium (H^3) has replaced stable deuterium (H^2).

To appreciate current and future work it is necessary to understand four concepts of physiologic importance that have been developed largely through the use of isotopes. These are turnover, space, mass and the precursor-product relationship.

The concept of *turnover* is related to the steady state and should be applied ideally only when it can be assumed that the system under observation is temporarily at equilibrium. Since it is not always possible to make this assumption in clinical studies, it is appropriate to consider measured values for *turnover* as first approximations of the real situation. *Turnover* is an expression of the movement, or the exchange, of substances between the various compartments of the body, or within a single compartment (e.g., the blood). The term may also be applied to the movement of the tracer in metabolic interconversions that are known to occur. The process of *turnover* is expressed mathematically in two ways, as (1) *turnover time*, and (2) *turnover rate*. The *turnover time* is defined as the time required for the appearance (or synthesis), *or* the disappearance (or utilization) of an amount of a substance equal to the amount present in the body, or in one of its compartments, at the start of an experiment. A graph of the type of data needed for the calculation of *turnover time* is shown in figure 3. This example has been taken from a study in which protein-bound radioiodine was injected intravenously, and samples of blood were taken thereafter at

* An excellent account of the early biologic application of isotopes is Hans Clarke's lecture [3] at the Wisconsin Symposium on Isotopes, 1946.

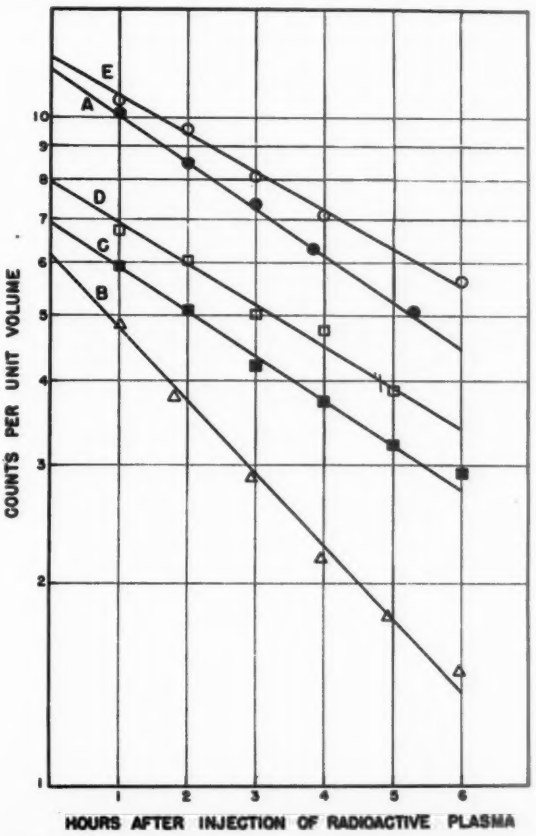

FIG. 3. Reasonable data for estimation of turnover time of protein-bound radioiodine. Plasma from one dog injected with I^{131} was given intravenously to five other animals whose thyroids were blocked with stable iodide. Rate of disappearance of radioactivity from blood of recipients is equivalent to utilization. (From *Application of Radioactive Iodine to Studies in Iodine Metabolism and Thyroid Function,* by I. L. Chaikoff and A. Taurog, a symposium on "The Use of Isotopes in Biology and Medicine," The University of Wisconsin Press, Madison, Wisconsin, 1948, published with the permission of the copyright holder.)

hourly intervals. The radioactivity of each sample was plotted logarithmically against time. Since the disappearance of the radioiodine from the plasma was due to utilization, it occurred in an exponential manner, and the plot is a straight line. The time required for the radioactivity to change by a factor of 2, the half-time, can be read off the plot. The half-time, multiplied by the natural logarithm of 2 ($\ln 2 = 1.44$), equals the *turnover time.*

The *turnover rate* is obtained by dividing the total amount of the substance in the system by the *turnover time.* The total amount of the sub-

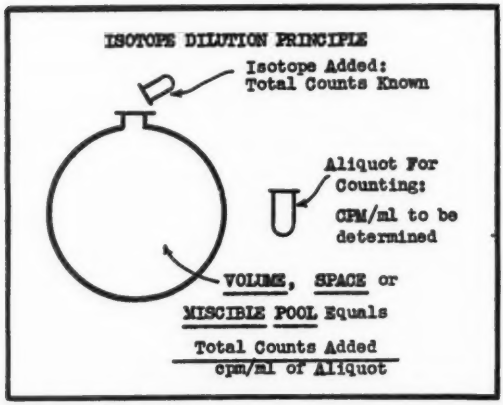

FIG. 4. Simplified diagram to illustrate one application of the principle of isotope dilution analysis.

stance in a system may either be known because one has administered a measured dose, or may be determined independently by the isotope dilution method (see below). An excellent example of a turnover study is Pinson's work [4] with tritium-labeled water (THO). Within a few hours of ingestion, or injection, THO is equally distributed throughout all the water of the body. Thereafter, the decline in the specific activity * of the plasma water becomes exponential. In a 70-Kg. man the turnover time for water is approximately 14 days, and the turnover rate is about 3.3 L./day. The values reported by Pinson, using tritium, are in good agreement with data on water turnover obtained with deuterium.

The next two concepts, *space* and *mass,* are related and their determination depends upon the principle of isotope dilution. The isotope dilution method enables one to estimate the volume (*space*), or the total amount of a substance in solution (*mass*), of a system that cannot be measured directly. Imagine a vessel of unknown volume that contains a solution of sodium chloride, the concentration of which can be determined (figure 4). A carefully measured amount (expressed in units of radioactivity: net counts per minute, or microcuries) of radioactive sodium chloride is added to the vessel and allowed to mix thoroughly with the original contents. An aliquot is removed for radioassay, and the net counts per minute (cpm) per milliliter are determined. The volume of the original solution is then equal to the total cpm added to the vessel divided by the cpm/ml. of the sample tested. The value for volume thus obtained may be called the *space,* the *miscible pool,* or the *volume of dilution.* In the case of the vessel in the example, the result is the *actual volume.* If one wishes to know the exact

* The term "specific activity" means the amount of labeled substance, expressed in units of radioactivity per unit of substance. In human tracer studies, the appropriate units are usually microcuries per gram (μc/gm.), microcuries per millimol (μc/mM), etc.

amount of sodium chloride in the vessel, one simply multiplies the volume (or *space*) by the concentration of the non-isotopic sodium chloride expressed in grams/ml. This value is called the *mass* of sodium chloride. It is perfectly proper to express the size of the miscible pool in units of *mass,** as grams or milligrams, rather than in units of *space,* as liters or milliliters. In the case of the imaginary vessel, the *mass* (or the miscible pool) is the actual number of grams of sodium chloride that are present.

These concepts of *space* and *mass* are fundamental for many clinical studies employing radioisotopes, and the clearest treatment of them for this purpose has been presented in the work of Burch's group at Tulane.[5] In clinical studies of electrolytes, or of a metabolite such as uric acid, that are distributed throughout many compartments of the body, only serum and urine are readily available for analysis. In this circumstance, it is convenient to express *space* and *mass* in serum equivalents. A serum equivalent is the *space* or the *mass* that the tracer would occupy if all of it in the body were present in the same concentration as the tracer in the serum. By application of the isotope dilution principle, it is possible to determine the total amount of a substance in a particular compartment of the body, or in the whole body. In the case of many substances, electrolytes and metabolites, there is a free exchange between all compartments, and it is often desirable to estimate the size of the exchanging pool. This may be calculated if one measures the daily intake of the non-isotopic substance involved, and the *turnover rate* as determined by a tracer study.

An example of the application of these principles is the recent studies of uric acid in gout. Stetten [6] used N^{15}-labeled uric acid, and Talbott's group [7] used C^{14}-labeled material to determine the size of the miscible pool, that is, the total amount in the body. Stetten's results were expressed in milligrams, so he was measuring what we have defined as the *mass.* In patients with gout the uric acid pool may be from 100% to 1,000% greater than it is in normal individuals. This, then, can be considered as a new biochemical criterion for diagnosis of gout, which is more precise than estimates of the serum uric acid concentration. Further studies demonstrated that the patient with gout has a metabolic abnormality in the synthesis of uric acid. The gouty individual deflects nearly three times as much of his dietary glycine into the production of uric acid as is the case in the normal subject. Since the rate of excretion of uric acid is not significantly elevated in gout, it is not surprising that the increased rate of synthesis results in deposits of crystalline urate in certain tissues.

We consider next the fourth concept, the *precursor-product relationship,* that is almost entirely a result of research with isotopes. Until isotopic methods were developed, biochemists used indirect methods and intuitions to chart the metabolic pathways for critical chemical substances. It was natural to assume that modification of the parent molecule would be the

* The reader who is trained in physics will recognize that this usage of *mass* is a convention, and does not have the same connotation as mass in the physical sense.

usual process, and ingenious patterns were inferred from the structural formula, from isolated enzyme systems, and from plausible chemical reactions. The early studies with heavy water and with the stable isotopes of nitrogen and carbon completely revised the intellectual structure of biochemistry and physiology. It is now evident that complex organic substances are seldom synthesized from compounds of a similar complex configuration. In most cases they are manufactured from small, simple units such as acetate, glycine, ammonia, carbonate and the like. The small building blocks that the body uses result from the rapid breaking apart by cellular enzymes of the complex organic substances that are consumed as food. In the conceptual sense, the body contains a series of "metabolic pools" of simple items, such as acetate and ammonia, to which are added fragments from the dietary, and from which the body cells obtain building blocks for their characteristic synthesis. A striking example of the contrast between the old and the new formulations is uric acid. The "pathway" for the for-

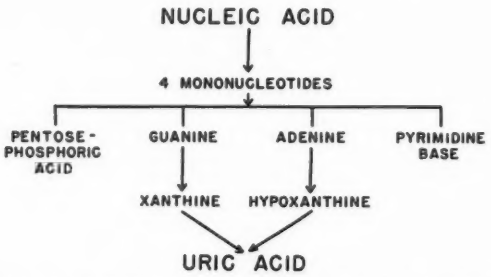

FIG. 5. A scheme for the formation of uric acid by degradation of nucleic acids by known enzyme systems. (Taken from Starling's *Physiology*, 1936.)

mation of this substance, as given in Starling's *Physiology* (1936), is shown in figure 5. The actual origin of uric acid from glycine, ammonia, acetate and bicarbonate—small building blocks from their respective metabolic pools—is shown in figure 6. As a result of isotopic studies of gout by several investigations, the origin of each carbon and nitrogen atom of uric acid is now known.[8] The central component of the compound is glycine, and, as noted above, the fraction of dietary glycine that goes into uric acid is abnormally high in the case of gout. The diagram reproduced in figure 6 could not have been drawn except as the result of tracer studies that permit the investigator to identify the actual precursors of the chemical compound.

The precursor-product relationship in the case of uric acid is a complex one, involving four distinct components. The relationship is much simpler in the case of cholesterol, which apparently has a single precursor, acetate. This two-carbon molecule is of increasing interest in studies of metabolism because of its great biochemical activity, and because it provides two-carbon

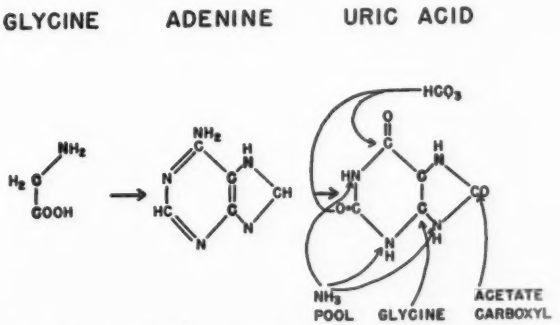

FIG. 6. The scheme for the formation of uric acid from small intermediaries from the metabolic pool. This diagram is the result of the independent work of several groups of investigators, who have identified the origin of each C and N atom. The central position of glycine is indicated by the heavier lettering. (From Stetten.[6])

units for many compounds. It is now established that, except for that of dietary origin, all the body's cholesterol is synthesized from acetate. In figure 7 the structural formula of cholesterol is shown, with each carbon atom identified with respect to its origin from either the carboxyl or the methyl group of acetate.[9] Since acetate is believed to be the sole precursor of cholesterol, and since the plasma cholesterol is in equilibrium with cholesterol synthesized in the liver, it is possible to estimate the rate of cholesterol formation in man following the administration of C^{14}-labeled acetate. Current studies in our laboratory have demonstrated the usefulness of a clinical test based on these facts.[10] After the administration of labeled acetate, the peak value for labeled plasma-free cholesterol occurs at about four hours. As a first approximation this peak value is a measure of the rate

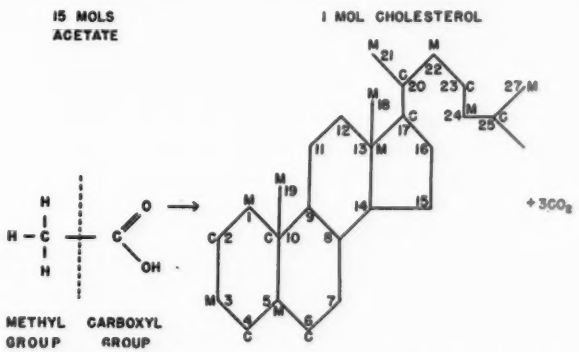

FIG. 7. The biosynthesis of cholesterol from acetate. The locations of the ring carbons derived from the carboxyl group are indicated by "C"; those derived from the methyl group of acetate are indicated by "M." (Adapted from Lieberman and Teich, figure 3, Pharmacol. Rev. 5: 285, 1953.)

of cholesterol synthesis, with high values indicating rapid synthesis, and vice versa. An example is given in figure 8, where the solid line is the specific activity-time curve for a normal individual, and the broken line is for a patient with untreated myxedema. In the latter case, cholesterol synthesis is greatly reduced, a finding that is in agreement with the observation that the *turnover rate* of cholesterol in myxedema is less than one fourth of the normal rate.[11]

The *precursor-product relationship* can be utilized in a variety of ways in clinical studies. Single doses of known or suspected precursors can be given, and the presence of the label used to identify or quantitate the product. Another useful procedure involves repeated administration of the precursor until isotopic equilibrium is achieved between the concentrations of precursor

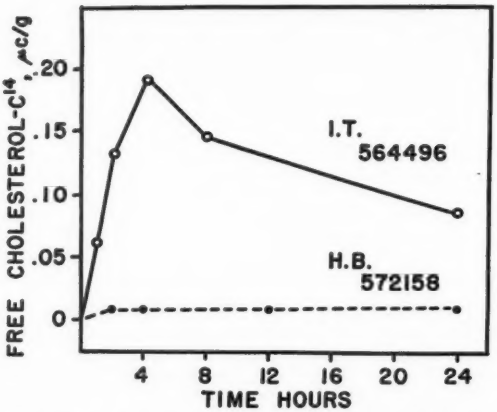

FIG. 8. The synthesis of cholesterol-C^{14} after an oral dose of 100 μc of 1-C^{14}-acetate. The solid line is the specific activity time curve of a euthyroid subject; the broken line is from a patient with myxedema, and shows no measurable synthesis of cholesterol.

and its products. The relation between the specific activities of the various compounds at this time will provide significant information on metabolic processes. When the administration of the precursor is stopped, very accurate estimates of turnover of the labeled products can be made. In fact, this was the design of some of the early, classic studies performed with heavy water and heavy ammonia.

In our laboratories, we have conducted combined experiments involving the daily feeding of cholesterol labeled with tritium, and a single administration of the cholesterol-precursor acetate. The acetate was given a few hours before adrenalectomy or oophorectomy was performed. Urine obtained at appropriate time intervals was fractionated, and 17-ketosteroids or estrogens were isolated. These corticoids contained both the tritium label and the carbon-14. Plasma cholesterol and cholesterol extracted from

the adrenal or the ovary also contained both labels. The relationship between the specific activities of these substances is being investigated in an attempt to extend our understanding of the metabolism of the steroid hormones.

Enough has been said about the precursor-product type of experiment to indicate that it offers a large and profitable field for clinical research. Experiments in which the radioisotopes of carbon and hydrogen are used can be designed to explore virtually any aspect of biochemical dynamics. The pioneer studies with deuterium and carbon-13 revolutionized our knowledge of metabolism, but they were so difficult to carry out that few clinical investigators attempt to conduct comparable studies. The technical methods now available for the measurement of tritium and radiocarbon are reliable and sensitive enough to permit clinical research with permissible doses of either isotope. All the beautiful and intricate studies that were initiated by Rittenberg and Schoenheimer with deuterium can now be extended to man. It is still necessary to use stable nitrogen (N^{15}) where the behavior of the N atom is critical, but in many cases the work can be done with compounds properly labeled with C^{14}, or with tritium. Clinical research will be advanced greatly as the use of these new methods is expanded.

In this paper I have attempted to offer simple formulations and examples of the important concepts that are the basis for advanced research using isotopes. Much of the literature on the subject presents a forbidding aspect to the clinician because of the mathematics involved. Unfortunately, it is not possible to avoid arithmetic and logarithms if one chooses to work with isotopes, but it is possible to resolve the mathematical aspects and the concepts they describe into relatively simple terms. It is certainly worth while to make the effort to understand the concepts, since they are the basis of much of the important contemporary clinical research. The investigators who are using isotopes to explore and explain metabolic processes in man are revolutionizing our knowledge and are rewriting our textbooks. It is necessary that we appreciate what they are doing.

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TREATMENT OF ACUTE AND CHRONIC LEAD POISONING WITH DISODIUM CALCIUM VERSENATE *

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UNTIL recently the treatment of lead intoxication has been generally unsatisfactory. The rapid in vivo breakdown of citrate precludes its usefulness as a lead complexing agent.[1] BAL is also ineffective, and there are suggestions that the BAL-lead complex may be toxic.[2] Calcium diets, acidifying agents, disodium hydrogen phosphate and other forms of therapy have met with varying success, but in the main they have not proved to be of predictable worth. The availability of disodium calcium ethylenediamine tetra-acetate † (Ca EDTA), a relatively new metal chelating agent which enhances the urinary excretion of lead, offered for the first time considerable promise in therapy of lead intoxication.[3, 4, 5] The parent compound, ethylenediamine tetra-acetic acid (EDTA), is a synthetic polyamino polycarboxylic acid. Its tetrasodium salt forms a stable, water-soluble, non-ionizable ring complex with a variety of metallic ions (figure 1). The phenomenon of binding such ions in non-ionizable complexes is termed chelation, and the end product is a metal chelate. The successful employment of chelating agents in industry for the control of undesirable cations in solution suggested their use as a means of mobilization of certain toxic metallic ions in man.

There is a definite order of preference for the binding of cations by EDTA. The alkali metals (Na and K) are held most weakly; the alkali earths (Ca, Mg), and the rare earths and di- and trivalent cations (Cu, Ni, Pb) follow in increasing degree of chelate stability. In general, the tendency for chelation is directly proportional to the pH and valency of a particular ion. As one would expect, in view of the chelation preference, when unbound EDTA is administered rapidly to animals and humans, the serum calcium decreases and tetany may ensue.[6] When administered as the preformed calcium chelate (Ca EDTA), however, serum calcium levels remain unchanged (figure 2).[7] The calcium ion of Ca EDTA is readily replaced by lead, copper, nickel and cobalt because of the greater stability constants of these heavy metal chelates (table 1).

Studies in animals suggest the upper limits of the dose of Ca EDTA given intravenously in man to be in the range of 0.5 gm. per 30 pounds of body weight per hour, or 1.0 gm. per 30 pounds of body weight per 24

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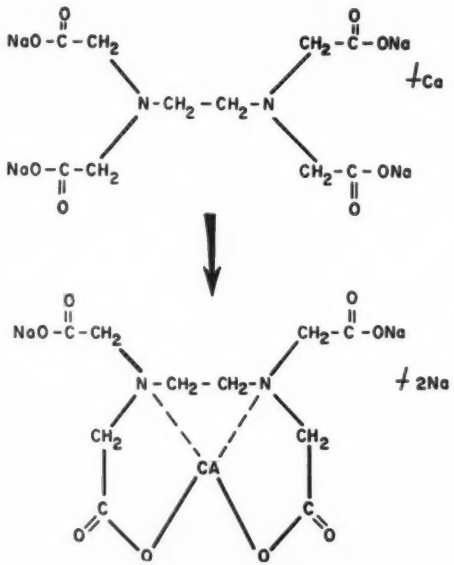
From the Department of Medicine, Medical College of Alabama, Birmingham, Alabama, and the Medical Service, Veterans Administration Hospital, Birmingham, Alabama.
† Kindly supplied by Bersworth Chemical Co., Framingham, Massachusetts.

hours.[8] Individual courses of treatment should be limited to 10 days, with a maximal dose of 7.5 gm. per 30 pounds of body weight.

Ninety-five to 98% of unchanged carbon labeled Ca EDTA is recovered in the urine six hours after intravenous administration.[9] The only reported toxic effect of Ca EDTA or other metal chelates in therapeutic doses in animals or man has been a decrease in prothrombin activity in one patient with preëxisting liver disease.[10]



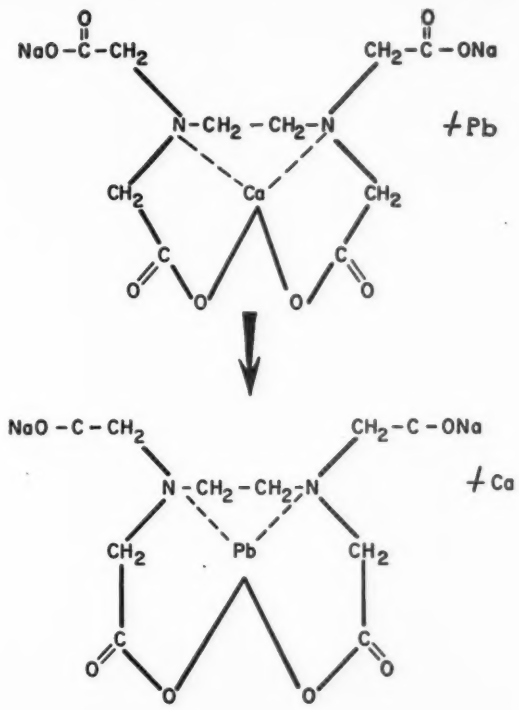
TETRASODIUM SALT OF ETHYLENEDIAMINE TETRA-ACETIC ACID AND ITS CALCIUM CHELATE

FIG. 1. Calcium chelation: the formation of disodium calcium ethylenediamine tetra-acetate (disodium calcium versenate or Ca EDTA) from the tetrasodium salt of ethylenediamine tetra-acetic acid.

This report deals with experience in the treatment of five cases of lead intoxication with Ca EDTA. The source of lead in two patients was from ingestion of an alcoholic drink distilled in a car radiator. Analysis of this whiskey revealed a lead concentration of 75 mg. per liter. Figure 3 shows the results of bubbling H_2S through the beverage: a heavy precipitate of lead sulfide has collected on the bottom of the tube. The remaining three patients were employees in a lead battery smelting plant.

METHODS

All patients were hospitalized and the diagnosis of lead intoxication was confirmed by quantitative urinary lead analysis. Twenty-four hour urine



DISODIUM CALCIUM VERSENATE AND DISODIUM LEAD VERSENATE

FIG. 2. Formation of disodium lead versenate from disodium calcium versenate. The calcium ion is readily replaced by lead, copper, nickel, cobalt and many other metallic ions.

lead excretions of 0.10 mg. per liter or higher were considered to be abnormal.

Total 24 hour urine outputs were collected in glass-stoppered Pyrex bottles which had been washed and rinsed with nitric acid and washed several times thereafter with double distilled water. A standard wet ashing pro-

TABLE 1

Stability Constants of EDTA Chelate Compounds

	Log K_{12}
Cu EDTA	18.40
Ni EDTA	18.40
Pb EDTA	18.20
Co EDTA	16.10
Ca EDTA	10.59
Mg EDTA	8.69
Na EDTA	1.66

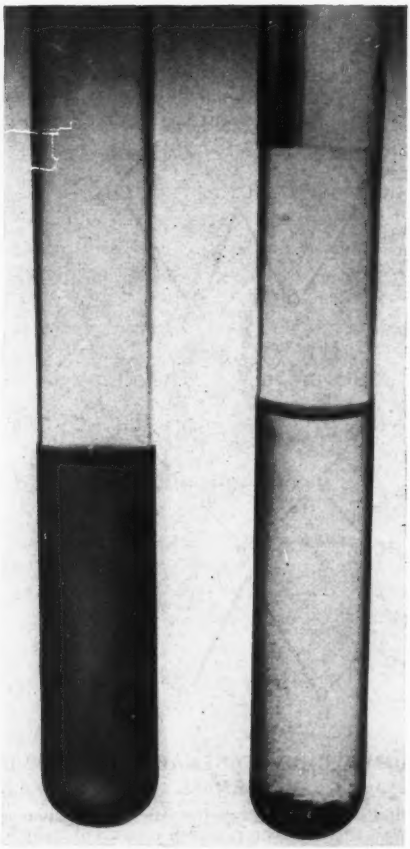


FIG. 3. Precipitation of lead sulfide, right tube, from whiskey distilled in a car radiator. Hydrogen sulfide was bubbled through the original beverage seen in the left tube.

cedure was used to rid the urine of organic materials, and lead analysis was then performed by a single extraction, mixed color dithizone method.[11]

Daily 24 hour urine collections were assayed before, during and after treatment for lead content.

Qualitative urinary coproporphyrin III was determined by Watson's method.[12] As a semi-quantitative measure of urinary coproporphyrin III, fluorescent units were arbitrarily obtained by comparing an aliquot of each 24 hour specimen in a Beckman photofluorometer using distilled water as a control of zero.

Venous blood samples were drawn before, during and after treatment for the following determinations: complete blood counts, serum calcium,

TABLE 2

Patient	I. A. S., 32 yr. old Negro male. Alcohol ingestion. Acute abdomen (steady, noncolicky pain), anemia, hypertension, headache, gingival lead line.	II. J. W., 45 yr. old Negro male. "Liquor"; colicky abdominal pain, anemia, lead line.	III. F. E., 30 yr. old white male, battery burner. Colicky pain, gastroenteritis, tremor, ataxic, delirium, anemia, hypertension, lead line.	IV. D. F., 25 yr. old white male, battery burner. Anorexia, abdominal fullness, tremor, insomnia, anemia, fatigue, lead line.	V. B. V., 43 yr. old white male, battery burner. Mild crampy abdominal pain, lead line.
Total EDTA (gm.)	15.5	14	18	20	7.5
Days of therapy	10	16	9	10	6
Urinary lead (mg./L.)					
Control	0.8	0.17	0.22	0.56	0.21
Maximal	21.1	15.1	6.1	7.5	3.64
End of therapy	0.96	0.97		0.4	0.04
Disappearance of symptoms after beginning therapy	2 hours	Before Rx begun	4 days	2 days	2 hours
Disappearance of lead line (days)	7	Persisted	9	5	5
RBC Basophilic stippling (cells/1,000 RBC)					
Pretreatment	19	6	3	12	1
End	0	1	0	0	0
Serum indirect bilirubin (mg.%)					
Pretreatment	1.2	0.25	0.50	0.75	0.4
End	0.25	0.25	0.25	0.25	0.2
RBC Osmotic fragility			Begin End	Begin End	Begin End
Control			Control .44 .34	Control .44 .30	Control .44 .34
			Patient .36 .28	Patient .42 .28	Patient .42 .30
End			Unchanged	Control .44 .30	Control .44 .34
				Patient .44 .24	Patient .42 .32
Urinary coproporphyrin III	Increased	Increased	Increased	Increased	Increased

phosphorus, chlorides, potassium, sodium, urea nitrogen, CO_2 combining power, prothrombin time, bleeding and clotting times, quantitative bilirubin, red cell osmotic fragility, and basophilic stippling per thousand red cells. Daily urinalyses and periodic physical examinations were done.

The drug was given by the intravenous route in a daily dose of 0.5 to 2.0 gm. in 500 ml. of normal saline over a period of one to two hours. The patients received an average total dose of 15 gm. over a 10 day period of therapy (table 2).

Results

As shown in table 2, the urinary excretion of lead was increased more than fifteenfold in all patients by Ca EDTA. Daily urinary lead values of case 1 are presented in figure 4. The increased lead excretion with each dose of Ca EDTA is typical of that obtained in each patient. Serial urinary lead determinations indicated a peak excretion occurring during the 12 hour period immediately following administration of a single dose of Ca EDTA; a minor effect persisted through the second 24 hour period.

Case 1, with acute lead intoxication, had the highest urinary lead content before and during treatment. This patient entered with acute, steady abdominal pain and a rigid abdominal wall. All signs and symptoms in this

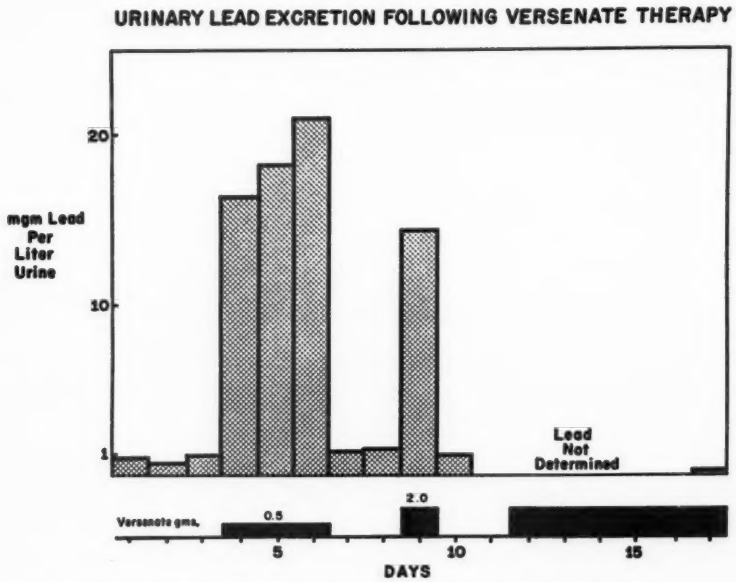


Fig. 4. Daily excretion of urinary lead in case 1 before and during disodium calcium versenate therapy. On the third day of Ca EDTA administration the urinary lead was increased more than twentyfold over control levels.

case and those of case 5 disappeared dramatically within two hours of the first injection of Ca EDTA. The colicky abdominal pain, tremor, confusion and ataxia of case 3 disappeared by the fourth day of therapy, and the anorexia, abdominal fullness, tremor and insomnia of case 4 were absent after the second day of treatment. Case 2 became asymptomatic prior to therapy.

The number of basophilic stippled red cells per thousand erythrocytes prior to therapy in cases 1 and 4 numbered 19 and 12, respectively; these completely disappeared within four and seven days of the start of therapy. In the other three patients stippled red cells were initially below 7 and fell to 1 or less with therapy.

In all save case 2, pretreatment indirect serum bilirubin levels were elevated and ranged from 0.4 to 1.2 mg.%. Normal levels of 0.25 mg.% or less were present after five days of treatment except in case 4, in whom the elevation persisted until the tenth day of therapy.

Pretreatment erythrocyte saline osmotic fragility studies revealed marked increased resistance to low osmotic concentrations of saline in case 3; increased resistance was still present when measured immediately after cessation of therapy. Less striking decreased osmotic fragilities were present in cases 4 and 5.

Qualitative urinary coproporphyrin III was elevated in all patients, pretreatment and post-treatment. Daily fluorescent units were obtained only in case 1. No precise correlation of daily urinary lead and coproporphyrin III excretions could be made.

All five patients had pretreatment gingival lead lines. Lead lines vanished during therapy (five to nine days) in all save one patient.

There were no observed alterations in any of the other tests. No toxic signs or symptoms were observed during or following therapy.

Discussion

The ability of Ca EDTA to chelate toxic soluble lead ions in vivo affords an effective method of therapy for lead intoxication. Due to greater affinity of Ca EDTA for lead ions, calcium is replaced by lead in the chelate ring and the resulting lead EDTA is rapidly excreted unchanged by the kidneys.

In our patients, lead diuresis produced by an average course of 15 gm. of versenate given over a 10 day period was accompanied by a series of spectacular effects. There was a rapid disappearance of such manifestations of lead intoxication as tremor, confusion, ataxia, headache, insomnia, hypertension, anorexia, diarrhea, abdominal pain, and signs of an acute abdomen. Lead deposits in the gums became no longer visible in all but one patient, and previously increased numbers of stippled erythrocytes and elevated indirect serum bilirubin returned to normal levels.

No toxic effects from Ca EDTA administration occurred. However,

it has not yet been conclusively demonstrated that EDTA will not inactivate metal containing enzyme systems as occurs in BAL poisoning. Lowered prothrombin activity has been reported in a case of hemochromatosis after Ca EDTA therapy.[10] None of the patients herein reported had previous liver damage, and their prothrombin activities were unaltered by therapy.

One of the patients was seen four weeks after completion of Ca EDTA therapy with an acute gonococcal urethritis. The urinary lead was elevated to 0.21 mg. per liter. Elevated urine lead concentrations several weeks after therapy as a result of acute infection or re-administration of Ca EDTA have been observed by others.[13] In the absence of reëxposure to lead, these findings demonstrate the inability of Ca EDTA, as given, to completely "de-lead" the body. In rats soft tissue lead is mobilized preferentially to bone lead.[8] The rapid disappearance in the above patients of soft tissue lead represented by the gingival lead line was notable.

Hemolysis due to increased erythrocyte mechanical fragility has been suggested as one of the mechanisms of anemia in lead intoxication.[14] Four of the patients reported here had evidence of hemolysis, as indicated by elevated indirect serum bilirubins. It was confirmed in this study that such hemolysis is not due to increased erythrocyte osmotic fragility, for the red blood cells actually were resistant to hemolysis in low salt concentrations. This decrease in osmotic fragility persisted throughout the course of therapy.

Urinary coproporphyrin III was elevated in all patients upon admission. Unlike the experience of Hardy et al.,[16] no fall occurred in the one patient during therapy with EDTA in whom daily urinary coproporphyrin III determinations were made. Increased coproporphyrin III excretion may be due to interference by lead with the conversion of coproporphyrin III to hemoglobin protoporphyrin.[15]

Summary and Conclusion

1. Five patients with acute or chronic lead intoxication successfully treated with calcium disodium versenate (Ca EDTA) are reported.

2. Ca EDTA produced a marked increase in urinary lead excretion which was maximal during the first 12 hours of therapy.

3. Loss of body lead into the urine was accompanied by:

(a) Rapid and striking amelioration of all signs and symptoms, including an "acute abdomen."
(b) Disappearance of gingival lead lines.
(c) Return to normal values of basophilic stippled red blood cells and serum indirect bilirubin; no immediate reversal of decreased erythrocyte osmotic fragility.

4. No toxic effects from Ca EDTA were observed.

5. Ca EDTA affords a safe and effective means of therapy of acute and chronic lead poisoning.

Addendum

Since this paper was submitted for publication we have successfully treated 14 additional patients with acute or chronic lead poisoning with disodium calcium versenate.

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NEPHROCALCINOSIS VISIBLE BY X-RAY ASSOCIATED WITH CHRONIC GLOMERULONEPHRITIS *

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IN 1947 Vaughan, Sosman and Kinney [1] presented a single unique case of nephrocalcinosis associated with chronic glomerulonephritis in which the calcification took the form of roentgenographically visible fine granular deposits throughout the renal parenchyma. Since that time only one other case, apparently identical in most respects, has been reported.[2]

It is our purpose to describe four additional cases of nephrocalcinosis associated with chronic glomerulonephritis, and to differentiate their roentgenographic findings from those in cases of nephrocalcinosis associated with other conditions.

Nephrocalcinosis is a term used in this report to designate roentgenographically visible fine diffuse calcification of the renal parenchyma. While larger foci of renal calcification such as may be seen with renal tumor, cyst or tuberculosis also may be classified as instances of nephrocalcinosis, our concern here is only with a finer and more diffuse type of renal calcification. Nephrocalcinosis of this latter variety has been described in a number of conditions (table 1). According to the findings in a recent review of the literature [3] of nephrocalcinosis, primary hyperparathyroidism is the disorder most commonly associated with nephrocalcinosis of the fine diffuse variety. Several authors [4-8] have described this type of nephrocalcinosis accompanying hyperparathyroidism in some detail. The calcification is usually of the size of a millet seed and is confined mostly to the medullary portion of renal parenchyma. This pattern may be so striking that the medullary portions of the kidney are clearly outlined on x-ray examination.[5-8] Microscopically the calcification is noted particularly in the lumina and epithelium of the collecting tubules and also in the surrounding interstitium. It is likely that this renal calcification is a consequence of the increased urinary excretion of calcium present in hyperparathyroidism. Underlying primary tubular damage caused by excess parathormone is probably not a factor in the process of calcification, since such a parathormone effect has never been conclusively demonstrated in man, although it has been noted in animals.[1] It should be noted that nephrocalcinosis as just described is not the only variety of renal calcification seen with hyperparathyroidism, renal stones actually being somewhat more common.[4]

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The syndrome of hyperchloremic acidosis (renal acidosis resulting from tubular insufficiency without glomerular insufficiency[10-16]) also has been associated with nephrocalcinosis, and according to Mortensen et al.[8] is second only to primary hyperparathyroidism in its frequency of association with x-ray visible nephrocalcinosis. In this condition also, calcium deposition tends to occur in the medullary portions of the kidney. The tubular defect is variously stated as inability to secrete $(H+)$ and (NH_3+),[16] with resulting loss of base, including calcium, or inability to reabsorb bicarbonate ion.[17] The initial cases of this group were reported in children,[10, 11] but more recently cases have been reported in adults.[12-15] The exact sequence of events leading to renal calcification is not clear in these cases. In some of the adult cases calcification seems to have occurred secondary to toxic tubular damage of sulfonamide origin,[13, 14] with the typical picture of hyperchloremic acidosis resulting from tubular insufficiency. That the nephrocalcinosis is not necessarily the primary underlying cause for the tubular

TABLE 1

Conditions Associated with Roentgenographically Visible Diffuse Nephrocalcinosis

A. *Most commonly associated*
1. Primary hyperparathyroidism
2. Hyperchloremic acidosis
3. Chronic pyelonephritis
4. Chronic glomerulonephritis

B. *Uncommonly associated*
1. Vitamin D intoxication
2. Prolonged ingestion of alkali and calcium
3. Sarcoidosis
4. Idiopathic hypercalciuria
5. Tuberculosis of bone

defects seen in this condition, and that it may represent a complication of the hypercalciuria in this base-losing disorder, is borne out by the fact that the syndrome of hyperchloremic acidosis may exist without renal calcification.[16]

Chronic pyelonephritis has been incriminated as the third most common condition associated with nephrocalcinosis.[8] Albright et al.[18] reported two such cases associated with *Hemophilus influenzae* infections of the kidney. Calcium deposits as a rule, however, when associated with pyelonephritis, tend to be larger and more unequal than those described with hyperparathyroidism and hyperchloremic acidosis, but occasionally may be of the fine diffuse type with which this report is concerned. In these latter instances the calcification would likely have taken place in sites of inflammation of the renal tissue, but adequate pathologic studies of this group of cases are not available. In our own experience, however, pyelonephritis is a relatively less common cause of diffuse nephrocalcinosis than has been reported.

In the previously mentioned review of the literature,[8] totaling 91 cases of

roentgenographically visible nephrocalcinosis, approximately 3% of these cases were found to be associated with chronic glomerulonephritis. It is with this apparently small segment of cases of nephrocalcinosis that this report is mainly concerned. Though chronic glomerulonephritis is very rarely accompanied by nephrocalcinosis, it is our purpose to point out that the roentgenographic appearance distinguishes this type of nephrocalcinosis from other conditions that are associated with diffuse renal calcinosis.

Other even less common causes of nephrocalcinosis which may be visible on x-ray, however, do exist. In association with vitamin D intoxication, calcification of the medullary portions of the kidneys has been described microscopically in a human subject,[19] but only one report in the literature reveals this renal calcification to be visible in premortem roentgenograms.[20] In addition, we have recently seen a similar second case. Sarcoidosis,[21] prolonged ingestion of alkali and calcium,[22] idiopathic hypercalciuria [8] and tuberculosis of bone [23] (table 1) also may rarely be associated with x-ray visible nephrocalcinosis. While nephrocalcinosis has also been reported to be present on microscopic examination in association with leukemia,[24, 25] widespread osteolytic carcinomatous metastases,[24–26] multiple myeloma,[27] pyloric obstruction with severe vomiting,[28, 29] prolonged ingestion of alkali,[30] mercury poisoning,[31a] and rarely with various other disorders, such as osteomyelitis, osteopetrosis, fractures and spinal cord lesions,[24, 25] we could find no reported instance in which roentgenographically visible calcification has been noted in these conditions. It would seem reasonable to expect that the degree of calcification occurring in association with these latter conditions may be marked enough in some instances to result in roentgenographically visible nephrocalcinosis if searched for. On the other hand, it has been demonstrated [32] that no close correlation can be drawn between the amount of histologic renal calcification and its visibility by x-ray. It would seem that there are other factors than the calcification, per se, probably having to do with parenchymal changes around the calcified sites, and the finite distribution of the collections of calcium that are important in determining whether microscopic calcification becomes roentgenographically visible. Therefore, it may be that the intimate and not yet fully appreciated details of the nephrocalcinosis accompanying hyperparathyroidism or the other conditions in table 1 are such that the lesions become readily visible by x-ray, while the over-all renal changes associated with the nephrocalcinosis of leukemia, for instance, are such that they will not produce x-ray opacity. Nevertheless, we have noted in one case of widespread osteolytic carcinomatous metastases, nephrocalcinosis visible on postmortem films of the kidney. No premortem films were available.

The following four case reports illustrate two proved and two probable cases of chronic glomerulonephritis associated with unusual and distinctive x-ray and microscopic findings that serve to distinguish these cases from other instances of diffuse nephrocalcinosis.

Case Reports

Case 1. Present Illness: A 27 year old white female nurse was first admitted to the Peter Bent Brigham Hospital in October, 1948. The patient had been in good health until 1940 when, at age 18, a routine urinalysis done for entrance to nursing school revealed a trace of albumin and 4 to 5 red blood cells per high power field. Blood pressure at this time was 110/80 mm. of Hg. Physical examination and all other laboratory tests were essentially unremarkable. Intravenous pyelograms done in January, 1941, were said to be normal. Phenolsulfonphthalein excretion was 55% in one hour, with an additional 10% in the second hour. During the next three years the patient consistently ran a trace of albumin and 4 to 5 white blood cells and red blood cells as well as rare granular casts in her urine. Blood counts were reported as normal. In 1944 she was rejected for Army service because of a heart murmur. The patient was quite asymptomatic for the following seven years.

In the fall of 1947 the patient was admitted to another hospital with complaints of headache, fatigability and ankle edema. Her urine at this time showed a rare red cell and 12 to 15 white blood cells per high power field, with 0.48 gm. % albumin per 24 hours. There was no anemia at this time. The nonprotein nitrogen was 38 mg. %. The phenolsulfonphthalein test showed 60% excretion in one hour and 80% in two hours. The intravenous pyelogram showed only faint dye excretion on the right. The patient was then placed on a low-salt diet, but her complaints persisted until her first Peter Bent Brigham Hospital admission a year later (October 1, 1948). There was no past history of childhood nephritis, frequent sore throats, or excessive alkali, calcium or sulfonamide administration. The patient had taken vitamin D to age 12 in apparently normal doses, but had drunk two quarts of milk a day for many years. No history of exposure to nephrotoxins could be elicited.

Physical Examination: Blood pressure, 230/140 mm. of Hg; pulse, 94; respirations, 12; temperature, 99° F. The patient was a well developed and well nourished adult female. The skin and mucous membranes were of good color and well hydrated. The fundi revealed grade III arteriosclerotic changes, with occasional fluffy white exudates and flame-shaped hemorrhages. There was slight haziness of the disc borders. The lungs were resonant throughout and revealed no abnormal breath sounds or râles. The heart was enlarged to 10 cm. from the midsternal line on the left in the fifth interspace, and a grade III apical systolic murmur could be heard. The rhythm was regular, and P_2 was louder than A_2. M_1 was increased. A systolic gallop was present. The kidneys were not palpable or tender. The rest of the abdominal examination was unremarkable. No ankle edema was present. The neurologic examination was normal.

Laboratory Data: Hinton test, negative. Red blood cells, 3.7 million. Hemoglobin, 12.4 gm.%. Hematocrit, 36. Sedimentation rate, 38 mm./hr. White blood cells, 7,600 mm.^{3} with a normal differential. Urine: pH, 5.5; specific gravity, 1.007 to 1.017; urine protein, 2 to 4 plus; 5 to 6 red blood cells and 3 to 5 white blood cells per high-power field. Sulkowitch test was negative on repeated examinations. Blood urea nitrogen, 32 mg.%. Nonprotein nitrogen, 72 mg.%. CO_2 combining power, 18.2 mM/L. Cl, 103 mEq./L. Total protein, 6.4 gm.%, with 4.3 gm. of albumin. Calcium, 5.3 mEq./L. Phosphorus, 1.5 mM/L. Alkaline phosphatase, 1.9 B. U. Sugar, 88 mg.%. Cholesterol, 340 mg.%. Urine culture showed enterococci on one occasion, and no growth on two others. Phenolsulfonphthalein test showed 5% excretion at 15, 30, 60 and 120 minutes, for a total of 20% in two hours. Urine specific gravity was 1.010 after overnight dehydration. The electrocardiogram was within normal limits. The cold pressor test revealed a rise in blood pressure from 230/120 to 260/150 mm. of Hg, while an Amytal sedation test revealed a fall in blood pressure from 200/120 to 140/100 mm. of Hg. The venous pressure was 60 mm. of saline, and the arm-to-tongue circulation was 16 seconds. The basal metabolic rate was plus 6.

X-rays: Abdominal films showed diffuse bilateral calcinosis of the kidneys apparently concentrated in the cortex of each kidney (figure 1). Intravenous pyelograms showed no visible dye excretion. Chest film revealed clear lung fields, with the heart size 25% above that indicated for the patient's height and weight. Skull films showed moderate hyperostosis frontalis and intact lamina dura.

Hospital Course: The patient was studied from the point of view of possible treatment of her hypertensive cardiovascular renal disease. Because of the presence of nitrogen retention she was thought to be not a good candidate for sympathectomy, and was discharged on a high carbohydrate, 50 gm. protein, low salt, alkaline ash, low calcium diet, with Amphojel and 20% ammonium citrate up to 30 ml. a day as tolerated. The latter medications were given with the hope of reducing the renal calcification.

The patient was admitted twice to the Peter Bent Brigham Hospital in the next three months for reëvaluation of her status. During this time her symptomatology,

FIG. 1. *Case 1.* Kidney film showing faint deposition of calcium in the renal cortex as indicated by the arrows. Kidneys appear normal in size. The degree of calcification is less advanced than in cases 2 and 3.

physical examination, laboratory data and renal calcinosis remained essentially unchanged except for the appearance of fresh hemorrhages and exudates in the fundi and a fall in hematocrit to 29.

In March, 1949, the patient, who had been getting along well symptomatically, suddenly developed severe headaches, convulsions, and coma, and died within a few hours after the development of these symptoms.

Autopsy: *

Gross Description: The body was that of a well developed young white adult female. Ears, eyes, nose and mouth were unremarkable.

Heart weighed 430 gm. There was slight hypertrophy of the left ventricular wall and its papillary muscles. Endocardium, valves and coronary vessels were not abnormal.

Lungs: Right weighed 590, left 780 gm. The cut surfaces showed a dependent congestion and were excessively moist.

* Performed at the New England Deaconess Hospital and reported through the courtesy of Dr. William Meissner.

Spleen weighed 180 gm. and showed evidence of mild congestion.

Pancreas, liver, biliary system and adrenals were essentially negative.

Kidneys weighed 200 gm. together and were of approximately the same size. The capsules stripped with difficulty. The renal surfaces were pinkish gray, finely granular and somewhat gritty when the cutting edge of the knife was run over them. The cut surfaces revealed markedly thinned cortices (0.4 cm.), which were also pink-gray and granular. The medullary pyramids, renal papillae, calyces and pelves were unremarkable. No renal stones were present. Renal arteries were free of degenerative changes. Ureters and bladder were normal.

Brain weighed 1,300 gm. At the base of the brain there was a massive subarachnoid hemorrhage investing the entire brain stem, including the pons, medulla oblongata, spinal cord and undersurface of the cerebellum. The posterior inferior cerebellar artery showed an aneurysmal dilatation, measuring 1.2 cm. in diameter, which had ruptured. There was a small amount of clotted blood in the third and fourth ventricles.

Thyroid and Parathyroid Glands: Not enlarged.

Microscopic Examination: Heart showed hypertrophy of muscle fibers, slight interstitial edema and an occasional polymorphonuclear and mononuclear cell.

Lungs: There were intense capillary congestion and early interstitial pulmonary edema.

Spleen showed congestion of the pulp and prominent arteriosclerosis.

Pancreas, liver and adrenals were unremarkable except for arteriosclerosis.

Kidney: Striking lesions were seen in the glomeruli and tubules, while the interstitial and vascular changes appeared to be secondary. Many of the glomeruli were completely obliterated by collagenous connective tissue. Others showed marked eccentric and concentric thickening of the Bowman's capsule by epithelial proliferation, so that the capsular space was obliterated and the glomerular tuft was shrunken and the capillaries were occluded. Still other glomeruli showed tuftal adhesions and distortion by marked lobulation, endothelial swelling and thickening of the basement membrane. Intimal thickening of many of the arterioles was noted. The interstitium of both cortex and medulla showed diffuse scarring and an accompanying infiltrate of mononuclear cells, plasma cells and lymphocytes. There was loss of tubules in some areas, with ectasia of other tubules. Very striking was the presence in the tubules of the cortex of numerous masses of dark blue-staining calcium granules (figure 2), varying in size from about 10 to 50 micra, particularly prominent in areas where hyalinized glomeruli were most numerous and interstitial inflammatory changes were noted. The calcification consisted mostly of calcium casts which lay within dilated tubular lumina, while the surrounding epithelium was atrophic or had entirely disappeared. In a few foci, however, necrotic tubular epithelium was present in which granular calcium deposits were noted. It would seem that the calcium was deposited primarily in tubular lumina rather than in tubular epithelium, although some evidence of the latter process was present. It was difficult to distinguish the specific part of the tubules involved in the process of calcification, but most of the deposition seemed to be in the loops of Henle, the distal convoluted, and the collecting tubules. Rare calcification was also seen in the collecting tubules of the medulla and in the interstitium of the cortex, but the glomeruli themselves were free of calcific deposits.

Brain: The aneurysm showed irregular fibrous collagenous thickening of its wall with focal deposits of lipophages. The elastica was very poorly preserved. Routine sections from the regions of frontal pole, central sulcus, calcarine fissure, third ventricle, striatum, hippocampus, pons, medulla, cerebellum with dentate nucleus were unremarkable except for the presence of blood in the subarachnoid space around the base of the brain. Except for the aneurysm, the vessels were conspicuously normal.

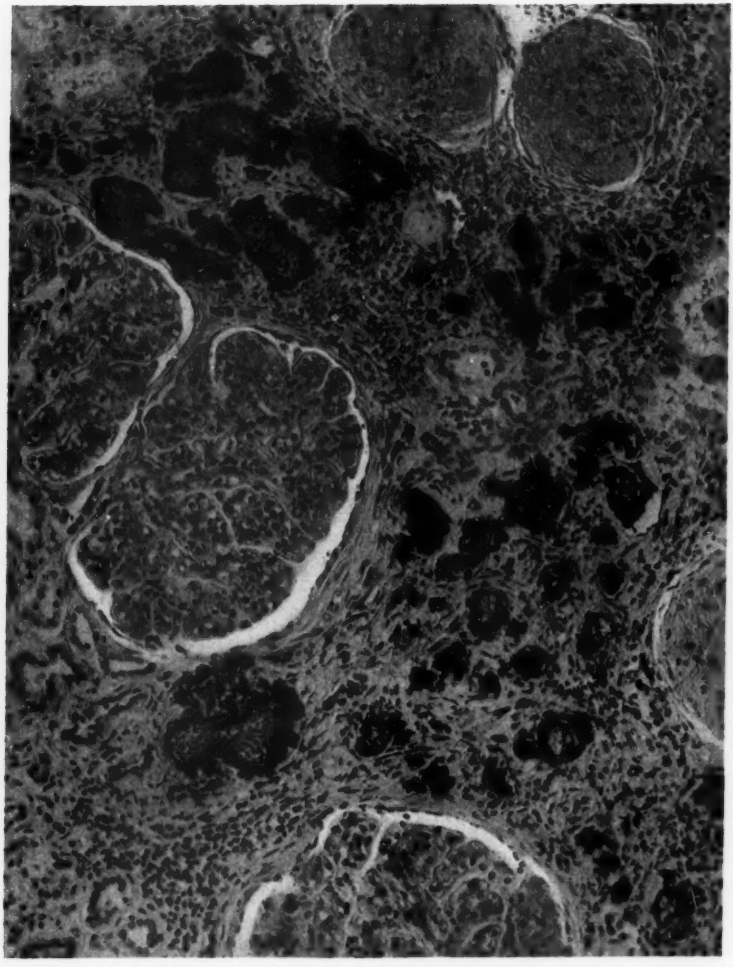

FIG. 2. *Case 1.* Renal cortex, ×100, demonstrating calcium deposition in the cortical tubules and the glomerular fibrosis and epithelial proliferation of chronic glomerulonephritis.

Parathyroids: There was no evidence of hyperplasia.

The final anatomic diagnoses were as follows: (1) Massive basilar subarachnoid hemorrhage following rupture of aneurysm of posterior inferior cerebellar artery. (2) Left ventricular hypertrophy. (3) Bilateral pulmonary edema. (4) Chronic glomerulonephritis with nephrocalcinosis. (5) Passive congestion of liver and spleen.

Case Summary: This young adult female had had a nine year history of chronic glomerulonephritis before she died suddenly of an unsuspected cerebral aneurysm. About one year before her death nephrocalcinosis, predominantly in the renal cortices, had been noted by x-ray. The patient had a history of a high calcium intake (two quarts of milk a day) for many years. Postmortem examination of the kidneys supported the diagnosis of chronic glomerulonephritis; the calcification was mostly in tubular lumina and less so in the walls of the tubules in the renal cortices.

Case 2. Present Illness: A 33 year old white married male machinist was first admitted to the Peter Bent Brigham Hospital in September, 1950, because of epigastric pain of four months' duration. Twelve years before admission, at age 21, the patient had noted the insidious onset of ankle edema. His urine at this time contained 4 plus albumin without cells, and the patient was told he had glomerulonephritis. He was placed on a restricted salt intake, but the edema recurred occasionally during the following seven years, once quite noticeably with periorbital swelling. He had noted cloudy urine and mild nocturia but no constitutional symptoms during this period. Four years before admission x-ray films of his kidneys were said to be unremarkable. Blood tests were also reported to be normal at this time. Three years before admission the patient was told he was anemic and was treated with liver, iron and vitamin B_{12}, without success. Two years previous to admission he was told his blood pressure was 200, and it had been elevated ever since. One year before admission the patient noted the onset of mild epigastric pain, relieved by food and rest but not by alkali. This pain had recurred four months before admission and had been troublesome since then. Headaches, epigastric tenderness and anorexia with occasional vomiting also had become quite severe during this period, and there had been a weight loss of 15 pounds. Two recent upper gastrointestinal series were reported to be negative. Just before admission the patient was again told that he had anemia and that his nonprotein nitrogen was 70. There was a past history of uncomplicated scarlet fever at age 14, lasting two weeks, and recurrent sore throats culminating in a tonsillectomy six years prior to admission. Milk intake in childhood was one quart per day. Since then he had averaged two glasses per day until eight months before admission, when he began to drink up to two quarts per day. Vitamin intake included cod liver oil in childhood and an occasional tablespoon with his children, but there was nothing to suggest excessive intake. There was no history of sulfonamide or excessive alkali ingestion. The patient had worked with cleaning fluid solvents of undetermined nature from the time his edema first appeared, and he had drunk quite heavily of beer and whiskey up to one year before admission.

Physical Examination: Temperature, 99.2° F.; pulse, 72; respirations, 14; blood pressure, 170/98 mm. of Hg. The patient was a well developed and well nourished, alert, nervous young male in no acute distress. He appeared chronically ill and had a marked uremic fetor. The skin was coarse and dry, and the mucous membranes and nails were moderately pale. The eyes had a uremic stare. The fundi revealed moderate narrowing and tortuosity of the arteries and grade I A-V nicking. The lungs revealed no abnormal breath sounds or râles. The heart was not enlarged but the apical impulse was forceful. A grade II systolic murmur could best be heard in

the third interspace at the left sternal border. A_2 was greater than P_2. No abdominal organs were palpable. Deep tendon reflexes were not remarkable.

Laboratory Data: Hinton test was negative. Red blood cells, 2,600,000. Hemoglobin, 10 gm.%; white blood cells, 6,500/mm.,[3] with 75% neutrophils, 18 lymphocytes, 3 monocytes and 1 eosinophil. There was moderate poikilocytosis on the smear. Urine pH was 5.5 to 6.0; specific gravity, 1.003 to 1.007; 1 to 3 plus proteinuria was present but no sugar; red cells varied from none to 15 per high power field on one occasion, and there were 3 white blood cells per high power field. Occasional granular casts were seen. Sulkowitch varied from slight trace to negative. Stool guaiac test was negative. Blood urea nitrogen, 72 mg.%; CO_2 combining power, 17.3 mM/L.; chloride, 107 mEq./L.; sodium, 140 mEq./L.; potassium, 5.4 mEq./L.; total protein, 5.7 gm.%, with an albumin of 4.2; calcium, 4.3 mEq./L.; phosphorus, 1 mM/L.; alkaline phosphatase, 2.9 B.U.; sugar, 82 mg.%; cholesterol, 298 mg.%. Urine culture report was not available. Phenolsulfonphthalein was 5% in 15 minutes,

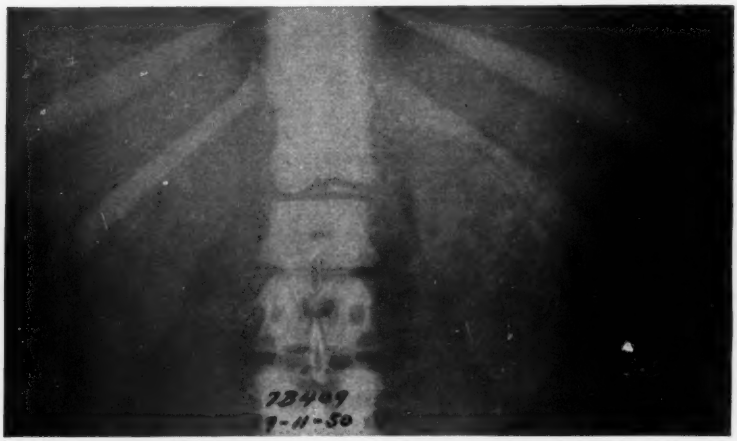

FIG. 3. *Case 2.* Kidney film showing both kidneys opacified by diffuse, finely granular calcium deposits predominantly in the cortices. Renal masses are slightly decreased in size.

5% in 30 minutes, 5% in 60 minutes, 5% in 120 minutes, for a total of 20% in two hours. Semiquantitative Addis count over a two-hour period revealed a total volume of 575 ml., with a specific gravity of 1.015, pH of 5.1, and 800,000 casts, 30,000,000 red blood cells and 10,000,000 white blood cells per 24 hours. An electrocardiogram revealed normal curves.

X-rays: Abdominal films revealed slightly small kidneys, with diffuse, irregular punctate areas of calcification scattered throughout both kidneys, but largely cortical in distribution (figure 3). No calculi were seen. Chest film showed a slightly enlarged heart with left ventricular prominence. X-rays of the skull, the lumbosacral spine and pelvis were normal. X-rays of the teeth showed an intact lamina dura. A gastrointestinal series showed active gastric and duodenal ulcers, the gastric ulcer being on the lesser curvature just proximal to the pylorus.

Hospital Course: The patient was placed on a dietary program aimed at the treatment of both his peptic ulcer and his renal disease. He was placed on a bland 2,200 calorie, 30 gm. protein, 3 gm. salt, low-calcium diet divided into six feedings, with added Gelusil and sodium bicarbonate frequently during the day. On this

regimen the patient improved markedly. His blood pressure came down to 125/90 mm. of Hg while he was in the hospital. On the eleventh hospital day the patient was discharged to his home at his own request on the above dietary regimen. Complete details of this patient's subsequent course could not be obtained. He evidently pursued a progressively downward course for the next one and a half years and died in uremia at another hospital where no autopsy examination was performed.

Case Summary: This 33 year old machinist had a fairly typical history of the insidious onset of acute glomerulonephritis, and his subsequent clinical course was highly suggestive of chronic glomerulonephritis. The protracted nature of the renal disease did not appear compatible with toxic nephritis related to possible exposure to nephrotoxins in the patient's work. X-rays revealed bilateral diffuse nephrocalcinosis preponderantly involving the renal cortices. The relatively high milk intake for eight months before admission was of interest in view of a similar finding in our other cases.

* *Case 3. Present Illness:* A 44 year old white married male electrician was first admitted to the Massachusetts Memorial Hospital complaining of episodes of nausea after breakfast of one and a half year's duration. This symptom had been present once or twice a week, often accompanied by vomiting of food. There was no associated pain. The patient always felt improved after vomiting of food, and was then able to continue with his work. For the year prior to admission he had also noted that when he became unusually tired or nervous (which happened one to three times weekly) he was troubled by a mild, dull, aching, dragging type of pain in the costo-vertebral angle regions posteriorly. The patient had had urinary frequency seven to eight times a day and one to two times at night for the past year. He never had been found to have hypertension. Two weeks prior to admission, because of continuation of postprandial nausea and vomiting, he consulted his local physician, who did a gastrointestinal series which was reported to be negative. These films, however, showed nephrocalcinosis of both kidneys, and the patient was accordingly referred to the Massachusetts Memorial Hospital.

The patient had had a tonsillectomy in 1908 at the age of four. There was no history of kidney disease, excessive vitamin D ingestion, sulfonamide administration, undue alkali ingestion or exposure to nephrotoxins. Sore throats had been frequent. For the past 20 years, however, the patient had had a considerable milk intake, consisting of a minimum of one quart a day and frequently up to three quarts a day. The patient stated he would frequently drink milk instead of water.

Physical Examination: Temperature, 98.6° F.; pulse, 80; respirations, 20; blood pressure, 180/100 mm. of Hg. The patient was a well developed, well nourished white male lying quietly in bed in no distress. The skin was warm and moist, with good turgor. There was no rash. Pedunculated nevi were present over the back. There was no significant lymphadenopathy. Examination of the head was unremarkable. The pupils were round, regular and equal, and reacted to light and accommodation. The extraocular movements were full and equal bilaterally. The fundi showed spasm of all arterioles. There was, however, no A-V nicking, hemorrhage, exudate or papilledema. Ears, nose and throat were unremarkable. The thyroid was not palpable. The chest was clear to inspection, percussion and auscultation. The heart was not enlarged, the rhythm was regular, and no murmurs were heard. P_2 was equal to A_2. The abdomen was soft and nontender. No organs or masses were felt. There was no tenderness in the costo-vertebral angles. No edema of the extremities was present.

* This case is presented through the courtesy of Dr. George Levene, of the Department of Radiology, Massachusetts Memorial Hospital.

Laboratory Data: Hinton, negative. Red blood cells, 3.65 million. Hematocrit, 31%. Hemoglobin, 9.9 gm.%. White count, 8,200, with 75% polys, 21% lymphocytes and 4% monocytes. Sedimentation rate, 32 mm. per hour, corrected to 9 mm. per hour. Urine specific gravity ranged from 1.007 to 1.015. There was a persistent albuminuria of 2 to 3 plus. On admission the urine was loaded with red blood cells and 4 to 6 white blood cells per high power field. Subsequently, all urine showed from 5 to 30 red blood cells and from 10 to 30 white blood cells per high power field. Nonprotein nitrogen, 62 mg.%; CO_2 content, 21.1 mEq./L.; chlorides, 95.9 mEq./L.; total protein, 5.8 gm.%; albumin, 3.4; globulin, 2.4; calcium, 4 mEq./L.; phosphorus, 1.3 mM/L.; alkaline phosphatase, 3.9 B.U. Stool guaiac test was negative. Urine culture revealed nonhemolytic *Staphylococcus aureus, Staph. albus,* diphtheroids, and nonhemolytic streptococci. Phenolsulfonphthalein test showed 3% of dye excreted in 15 minutes, 5% in 30 minutes, 5% in 60 minutes, and 5% in 120 minutes, with a total of 18% after two hours.

FIG. 4. *Case 3.* Roentgenogram revealing heavy diffuse deposition of calcium in the kidneys, again predominantly involving the cortices. Renal masses are only moderately decreased in size.

X-rays: X-ray films of the abdomen revealed bilateral diffuse calcification of the renal parenchyma, more prominent in the cortices (figure 4). The kidneys were normal in size, shape and position. No calculi were seen. Intravenous pyelograms revealed no visible excretion of Diodrast from either kidney. Chest film revealed a very small heart. Lungs were emphysematous; the bone detail was normal.

Clinical Course: The patient was entirely afebrile and asymptomatic throughout his hospital stay. He was discharged on a 50 gm. protein, low calcium diet. Unfortunately, no further follow-up could be obtained on this patient.

Case Summary: Although the exact etiology of the nephritis is not clear in this case, the history of frequent sore throats, the insidious development of the renal insufficiency, and the large number of red cells and albumin in the urine make it likely that there was underlying chronic glomerulonephritis with a superimposed pyelonephritis. There was diffuse nephrocalcinosis, much more prominent in the cortices, seen on x-ray of the abdomen. Also

of note was the 20 year history of excessive daily milk consumption (up to three quarts).

Case 4. Present Illness: A 24 year old college sophomore was first admitted to the Peter Bent Brigham Hospital in August, 1950, for evaluation of his renal status. At age five the patient had had an attack of acute hemorrhagic nephritis lasting several weeks. Following this illness his urine was clear for several years. He had never had scarlet fever, but at age 11 chronically inflamed tonsils were removed. One year later, 12 years prior to admission, the patient began to suffer from nocturia, polyuria, polydipsia and fatigability. The following year the patient was seen at another hospital, where he was found to have chronic renal insufficiency associated with a blood urea nitrogen of 35 mg.%, elevated serum calcium (8 mEq./L.), normal serum phosphorus and normal alkaline phosphatase. Urine examination showed a specific gravity of 1.010, with 1 plus albumin and a few white blood cells per high power field. Serum proteins were normal. X-ray examination of the skull and long bones revealed no evidence of decalcification. A surgical exploration of the neck for a parathyroid tumor was carried out. Only three parathyroid glands could be identified, but there was no gross evidence of tumor or enlargement of these glands. The right inferior gland was removed and subsequently examined at the Massachusetts General Hospital in consultation by Dr. Benjamin Castleman, who felt that it definitely showed secondary hyperplasia. A lymph node removed from the right mediastinum showed old, inactive tuberculosis. The patient was placed on a low-calcium diet, and when seen one year later his clinical condition was essentially unchanged. His blood chemistries at this time revealed a blood urea nitrogen of 24 mg.%, a serum calcium of 6.3 mEq./L. and a normal serum phosphorus.

In April, 1944, the patient's main complaint was still increasing fatigability; the polyuria and nocturia had persisted also. Laboratory examination of the urine showed a specific gravity of 1.014, with 21 white blood cells and 3 red blood cells per high power field, and 1.8 gm. of albumin per 24 hours. Sulkowitch test was 2 plus. Blood urea nitrogen was 53 mg.%; serum calcium was 7.0 mEq./L., and serum phosphorus was now slightly elevated, 1.9 mM/L. Skeletal roentgenograms were negative, but two renal calculi were noted on the left and the kidney shadows seemed somewhat smaller and denser than usual. Blood vessels in the leg were calcified. Exploration of the superior mediastinum carried out at this time revealed no evidence of a parathyroid tumor.

In 1946 blood and urine findings were essentially as before, with a blood urea nitrogen of 37 mg.%, a creatinine of 3.33 mg.% and a hemoglobin of 11 gm.%. The patient was maintained on a low calcium and phosphorus diet. Examination of the urine showed *Streptococcus faecalis,* for which penicillin and mandelic acid were given.

In 1948 the blood urea nitrogen was 72 mg.%; serum calcium, 6.6 mEq./L., and phosphorus, 1.6 mM/L. Because of symptoms referable to a ureteral calculus, a left ureterolithotomy was performed at another hospital and a calcium oxalate stone removed. Throughout the patient's course, albuminuria, pyuria and nocturia were present without high blood pressure, anemia or eyeground changes. The patient had lost weight gradually over the years and complained primarily of a lack of energy and a dry, itchy skin at the time of his admission to the Peter Bent Brigham Hospital in August, 1950.

Physical Examination: Temperature, 97° F.; pulse, 78; blood pressure, 140/90 mm. of Hg. The patient was a coöperative but somewhat lethargic young adult male who had difficulty following the trend of conversation and revealing the events of his illness. The skin was tanned and dry. The nail-beds and mucous membranes were slightly pale. No adenopathy was present. There was a questionable calcium deposit

in the left eardrum and there were palpable calcium deposits in both olecranon bursae. The fundi were normal. The lungs were clear to percussion and auscultation. The heart was not enlarged; its rhythm was regular and no murmurs were heard. P_2 was equal to A_2. There were no palpable abdominal organs. Rectal examination and genitalia were unremarkable. There were no significant neurologic changes.

Laboratory Data: Hinton, negative. Hematocrit, 48. Sedimentation rate, 20 mm./hr.; white blood cells, 4,700, with a normal differential. The smear was normal. Urine pH was 6. Specific gravity, 1.006 to 1.010. Protein, 2 plus; no sugar. The urine was loaded with white blood cells and occasional red blood cells, and hyaline and granular casts were seen. The urine volume varied from 1,000 to 2,500 ml. a day. Blood urea nitrogen, 47 mg.%. Nonprotein nitrogen, 82 mg.%. CO_2 combining power, 21.6 mM/L. Chloride, 94 mEq./L. Sodium, 142 mEq./L. Potassium, 5.3 mEq./L. Total protein, 6.6 gm.%, with an albumin of 5.4 and a globulin

FIG. 5. *Case 4.* Kidney film showing diffusely calcified renal masses with tiny stippled foci of heavier calcification and a thin outer shell of dense calcification. Kidneys are markedly decreased in size. The spleen is considerably enlarged.

of 1.2 gm.%. Calcium, 7.5 mEq./L. Phosphorus, 1.7 and 2.2 mM/L. Alkaline phosphatase, 2.5 B. U. Sugar, 64 mg.%. Cholesterol, 308 mg.%. Urine culture revealed *Staph. aureus,* nonhemolytic streptococci, and *Alcaligenes faecalis.* Phenolsulfonphthalein test showed no excretion in 15 and 30 minutes. Urine calcium excretion was 242 mg. in 24 hours on a low calcium diet. An electrocardiogram showed ST elevation in Leads II and III and a small Q_2, Q_3, and QAVF, with questionable peaking on one occasion of the T waves in Leads V_3–V_4. These changes were felt to be compatible with acute posterior myocardial infarction, pericarditis and possibly hyperkalemia, but there were no clinical or laboratory data to corroborate these possibilities.

X-rays: X-ray films of the abdomen revealed the renal masses to be slightly smaller than normal and much increased in density (figure 5). The kidneys were outlined by a thin shell of calcific density, with numerous fine irregular streaks and spots of calcific density internally amid the diffuse calcinosis. There was no particular localization of the calcification to any region of the kidney. The spleen was

slightly enlarged. Bone structure and density were normal. There was calcification in the vessels of the pelvis and in both tibial arteries. Chest film revealed a heart of normal size and minimal healed tuberculosis in the right apex and calcification in the arch of the aorta. The lamina dura was intact about most teeth, although this was lacking in some areas.

Hospital Course: The patient was placed on a low phosphorus, low calcium, 40 gm. protein, moderate salt diet plus aluminum hydroxide tablets to decrease phosphate absorption from the gastrointestinal tract. He received a seven day course of penicillin, 800,000 units a day, with subsequent clearing of his bacilluria. His blood pressure remained within normal limits, and the patient was afebrile during his hospital stay. On the eighth hospital day the patient was dialyzed on the artificial kidney for six hours, with transient lowering of the blood urea nitrogen from 70 to 36 mg.%. The patient's itching was markedly relieved and he claimed he felt better, but by the time of his discharge from the hospital he showed no significant improvement. His blood urea nitrogen at this time had again become elevated (to 89 mg.%). It was the feeling of the service that it was still possible, but unlikely, that the patient had primary hyperparathyroidism with secondary nephrocalcinosis and accompanying renal insufficiency, in addition to some degree of superimposed secondary hyperparathyroidism at this time. It was held more likely, however, that the patient had chronic glomerulonephritis with secondary hyperparathyroidism. The patient was discharged to his home on the eighteenth hospital day without further surgical exploration and on the dietary régime he had been on in the hospital.

The second and last admission to the Peter Bent Brigham Hospital was in November, 1953. During the two year interval between admissions the patient's old symptoms of pruritus, polydipsia, polyuria, nocturia, fatigability, weakness and recurrent renal calculi had steadily progressed. The patient was again admitted to the hospital, primarily for consideration of renal transplantation. On physical examination the findings were much the same as on the first admission except for a blood pressure of 165/110 mm. of Hg, numerous excoriations over the skin, and numerous subcutaneous nodules along the extensor surfaces of both forearms. Laboratory data revealed a hematocrit of 30, proteinuria of 1 to 3 plus, and up to 45 red blood cells and 25 white blood cells per high power field in the urine. Blood urea nitrogen was 135 mg.%. CO_2, 16 mM/L. Chloride, 105 mEq./L. Sodium, 140 mEq./L. Potassium, 6.4 mEq./L. Calcium, 5.1 mEq./L. Phosphorus, 4.2 mM/L. Uric acid, 12.2 mg.%. An electrocardiogram showed occasional evidence of left ventricular hypertrophy and high peaked T waves suggestive of potassium intoxication.

X-rays: Abdominal films showed the kidneys to be smaller than on the previous admission, and the scattered areas of calcification through both renal outlines appeared denser and more numerous than before. The bones showed slight coarsening of the trabecular pattern and hypercalcification. Examination revealed the heart to be 22% enlarged above the predicted average and definitely larger than during the previous admission. There were no lamina dura changes.

Because of the marked anemia the patient was given several transfusions of packed cells, which brought his hematocrit up to 37. On the eighth hospital day he showed evidence, both chemically and by electrocardiogram, of hyperkalemia; he was therefore dialyzed with the artificial kidney, with much improvement in his clinical status. On the thirteenth hospital day, following another episode of hyperkalemia treated by glucose and insulin, the patient had a kidney homograft carried out in his right thigh. Postoperatively, the patient became hypotensive and hyperkalemic once again. He died on the day following operation while being prepared for another hemodialysis.

Autopsy:

Gross Description: The body was that of a fairly well nourished and developed but somewhat pallid young white adult male. Old, well healed scars of the previous

parathyroid and mediastinal explorations were present. The homologous kidney transplant was in place in the right midthigh. The ears, eyes, nose and mouth were essentially unremarkable.

Heart weighed 330 gm. There was slight thickening of the left ventricle, but the valves and endocardium were not remarkable. Rather severe coronary artery sclerosis was present, but no thrombi or occlusions were noted.

Lungs weighed 400 gm. each. The pleura was smooth. The cut surfaces were gray-pink and well aerated, and gave the impression of spicules of calcified material against the sharp edge of the knife. Slight calcification of the tracheal rings was noted.

Spleen weighed 275 gm. Capsule was tense. On cut surface the white pulp appeared increased.

Pancreas showed no significant changes.

Liver weighed 1,925 gm. It was enlarged, firm and brownish in color.

Adrenals showed no significant changes.

Kidneys: The right kidney weighed 89 gm. and the left one 84 gm. Both kidneys were small and contracted, and the capsule stripped with difficulty, leaving a granular surface. There were numerous cysts containing clear fluid, up to 2 cm. in diameter, in both cortex and medulla. The cortex was thin, 2 to 3 mm., and poorly defined. On cut surface calcification was evident subcapsularly, through the cortex, and in the tips of the papillae. The renal arteries, particularly the one on the right, showed marked calcification and narrowing.

Thyroid showed no gross abnormalities.

Parathyroid: Two enlarged firm yellow glands were found.

Lymph nodes: The nodes around the pancreas, celiac axis and in the retroperitoneal and periaortic regions were enlarged and relatively firm, and on cut surface were pale, white and homogeneous.

Bone marrow was not abnormal.

Microscopic Examination: Heart: No abnormalities were noted except for intimal proliferation and fibrosis and hyalinization of the coronary arteries.

Lungs: There was slight pleural thickening. A few multinucleated foreign body giant cells were seen containing crystalline material which was doubly refractile on polarization and was identical with the crystals also found in the spleen and lymph nodes.* Several focal areas of calcification, in some of which the doubly refractile material could be seen, were present in the alveolar septa.

Spleen: There was hyperplasia of the white pulp with central activity. Large numbers of epithelioid cells and foreign body giant cells containing the previously described crystalline material were present. Many blood vessels showed hyalinization of their walls, with surrounding accumulations of epithelioid cells and giant cells.

Pancreas, liver and *adrenals:* Essentially unremarkable.

Kidney: The normal architectural pattern was almost completely destroyed by cystic, calcific and fibrotic processes. The capsule was thickened and there was subcapsular calcification. The cortex was very thin, and most of the glomeruli were partially or completely fibrosed. Some glomerular tufts and capsules showed epithelial proliferation, and in some instances the tufts were adherent to the capsules. Large cystic areas, apparently dilated tubules lined by tubular epithelium and full of calcified material, were present in the cortex. A few of the cysts showed evidence of calcification in their walls, and contained the doubly refractile crystalline material

* Tissue analyses utilizing paper chromatographic technics, nitroprusside and murexide reactions, melting point determinations, and solubility characteristics indicated that the crystalline material was not an amino acid, such as cystine, or uric acid. Spectrographic analysis of the crystals by Prof. Clifford Frondell revealed them to be composed as follows: 90 to 95% calcium oxalate dihydrate, 5 to 10% the monohydrate and less than 1% unidentified.

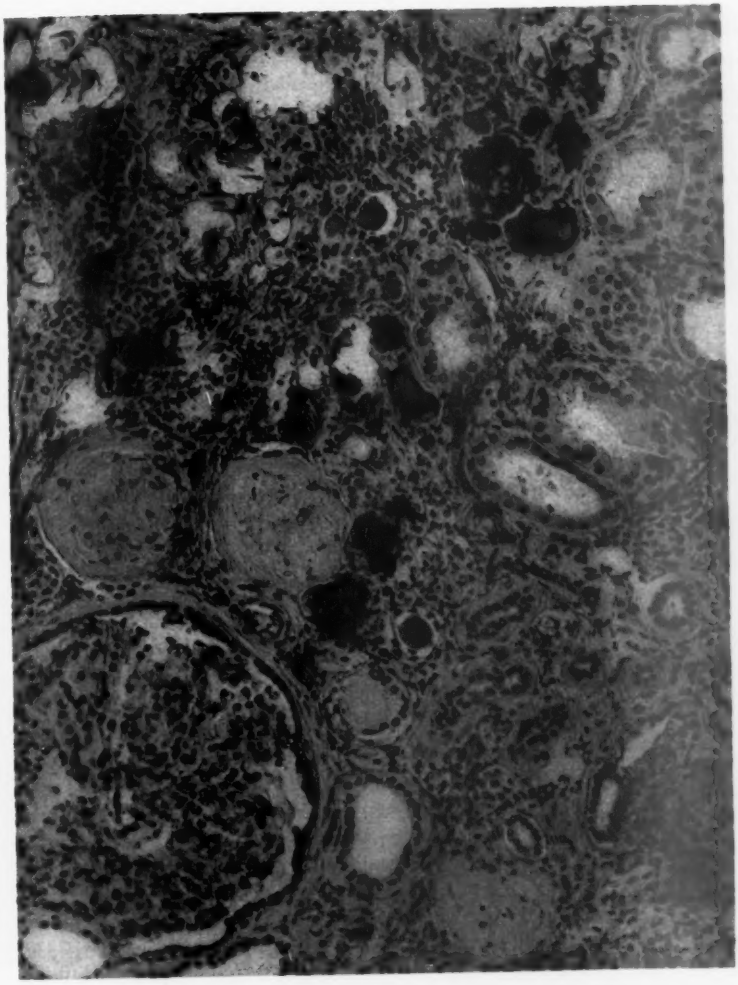

FIG. 6. *Case 4.* Renal cortex, ×100, illustrating the precipitation of calcium salts in the cortical tubules. Fibrotic and proliferative changes of chronic glomerulonephritis are apparent in the glomeruli.

previously described. Occasional deposits of this material also were present in the interstitium. Many tubules of the cortex had their lumina and lining epithelium completely effaced by calcium deposition (figure 6). There also were collecting tubules in the vicinity of the papillae which showed similar evidence of calcification. The predominance of the calcification, however, was in the cortex rather than in the medulla. In a few areas of the cortex underlying tubular damage was indicated by replacement of tubular epithelium by hyalinized tissue which showed little or no evidence of calcification. Many of the proximal convoluted tubules were dilated and contained hyaline casts. The arterioles showed slight thickening and fibrosis.

Parathyroids: The glands were composed of numerous closely packed dark vesicular cells having little cytoplasm, lying in an eosinophilic reticular network, and with fine vacuoles dispersed between them. The gland capsule was moderately thickened.

Thyroid showed no abnormalities.

Testis showed moderate atrophy of the seminiferous tubules and oligospermia.

Lymph nodes: Nodes from iliac, tracheal and pancreatic regions showed effacement of the normal follicular pattern by a chronic granulomatous process. This process consisted of focal areas of fibrosis and hyalinization intermingled with epithelioid cells and giant cells containing the doubly refractile crystalline material. A few foci of calcification also were present. Many of the cells lining the sinusoids were filled with yellow-brown finely granular pigment.

The final anatomic diagnoses were: (1) Chronic glomerulonephritis with nephrocalcinosis. (2) Parathyroid hyperplasia, secondary to renal disease. (3) Osteitis fibrosa, slight, secondary to hyperparathyroidism. (4) Calcification of the lungs and lymph nodes. (5) Chronic granulomatous inflammation secondary to crystalline material in kidney, spleen and lymph nodes. (6) Hemosiderosis of lymph nodes (secondary to blood transfusions). (7) Severe arteriosclerosis of aorta, coronary and renal arteries.

Case Summary: This 25 year old male apparently had had acute glomerulonephritis at age five. At age 12, shortly after the advent of polyuria and polydipsia, he was found to have nitrogen retention, elevated serum calcium, normal or slightly elevated phosphorus and normal alkaline phosphatase without bone changes. The patient was twice fruitlessly explored operatively for parathyroid tumors. At age 17 bilateral renal calcinosis was first discovered. The patient's blood chemistries conformed to the above pattern until his death. Clinically it was never clearly established whether his renal disease was primary or perhaps secondary to a hyperfunctioning parathyroid adenoma. Abdominal films revealed an unusual pattern of dense diffuse calcification of the renal masses, with a thin outer rim of even denser calcification. The patient died of renal insufficiency gradually increasing over a 15 year period. At autopsy the kidneys revealed changes typical of chronic glomerulonephritis, with calcification in the tubules of both cortex and medulla but predominantly in the cortex. Calcification of the lungs and lymph nodes also was noted. The systemic crystallinosis with an accompanying chronic granulomatous inflammation in the lungs, spleen, lymph nodes and kidney remains unexplained at present, but further crystallographic studies are being carried out. Dr. Dammin, hospital pathologist, did not consider the microscopic findings to be compatible with sarcoidosis.

Discussion

Calcification in tissues has classically been divided into the dystrophic and metastatic varieties. The dystrophic type applies to calcification in dying and devitalized tissue, while the metastatic variety applies to the calcification taking place in normal tissue. Various explanations of the chemical background for these processes have been put forth.[25, 33, 34] Thus, it is thought that the deposition of calcium phosphate is facilitated in necrotic tissue because of the lowered CO_2 tension and increased alkalinity of this tissue. On the other hand, metastatic calcification is held to be favored in normal tissue by an increase in serum calcium or phosphorus concentration, or both, by increased tissue alkalinity, and perhaps by a decrease in the protein content of the plasma. While the distinction between dystrophic and metastatic calcification has been rigidly drawn in the past, combinations of these processes have been found to exist in many instances of human tissue calcification,[24, 35] and indeed it is evident that this gross classification will have to be abandoned as the biochemical aspects of calcification become better understood.

It has also become apparent that the mechanisms responsible for local tissue calcification are complex and almost certainly depend on factors additional to those enumerated above. It is not our purpose to discuss in detail in this paper the theoretic aspects of tissue calcification, but only to point out in our cases those factors which may have some bearing on the renal calcinosis which was observed.

Four cases of chronic glomerulonephritis associated with a striking degree of nephrocalcinosis easily visible by roentgenograms have been described. In three of these cases the calcinosis predominantly involved the cortex, while the remaining one (case 4) revealed an unusual type of diffuse nephrocalcinosis, with no evident cortical or medullary localization by x-ray examination but somewhat more prominently involving the cortex on microscopic examination. In two of the cases histologic confirmation of the diagnosis of chronic glomerulonephritis was available, while in the other two the diagnosis was strongly suggested by the patient's history and clinical course.

The association of nephrocalcinosis visible by x-ray with chronic glomerulonephritis is uncommon, as previously noted, and represents only a small percentage of all cases of roentgenographic nephrocalcinosis. Even microscopic nephrocalcinosis associated with chronic glomerulonephritis is unusual. Detailed texts[31b, 36] on renal pathology make little or no reference to the association of these two conditions. Patrassi,[37] however, found microscopic evidence of calcification, mostly in the tubules of the cortex, in eight of 17 cases of chronic glomerulonephritis. Older case reports,[38, 39] reputed to show renal calcification in association with "nephritis," are difficult to interpret from the point of view of the type and etiology of the renal disease. It is apparent that more detailed pathologic studies are necessary

to demonstrate accurately the frequency of the association of microscopic nephrocalcinosis with glomerulonephritis. While there is a tendency for parenchymal calcification to occur in association with chronic glomerulonephritis, only rarely are the calcium deposits marked enough to be visible by x-ray.

Case 1 illustrates completely the association of chronic glomerulonephritis, proved histologically, with nephrocalcinosis confined almost entirely to the renal cortex microscopically and demonstrating a very distinctive cortical distribution by x-ray. This case is identical in all respects to the two previously reported similar cases,[1, 2] except that the previous observers did not emphasize the unusual cortical distribution of the calcium apparent on abdominal films. Histologic evidence in all three cases indicates that the calcification took place mostly in tubular lumina and to a lesser degree in the lining tubular epithelium. Only in our case is histologic evidence for underlying tubular damage cited. The tubular changes in our case almost certainly are related to the chronic glomerulonephritis. The frequent occurrence of frank tubular degeneration in glomerulonephritis is perhaps not widely appreciated, but it is well documented.[8,10] However, the high calcium intake of our patient and of the other reported cases [1, 2] may have played an additional rôle in the renal calcification. It is further of interest to note the case of Wermer, Kuschner and Riley,[40] in which the renal calcinosis was attributed to a high milk and alkali intake and in which a chronic glomerulonephritis was discovered at autopsy. On microscopic examination the calcification was again mostly cortical in distribution. No renal x-rays were described. The close similarity of this case to our case 1 is apparent.

In cases 2 and 3 pathologic study of the kidneys could not be carried out, and the diagnosis of chronic glomerulonephritis in both instances rests on highly suggestive clinical evidence. The cortical distribution of the calcinosis was again noted on x-ray examination, as in case 1. Of interest also is the history of excessive milk ingestion in both these patients, for eight months in one instance and for 20 years in the other. Serum calcium and phosphorus values were normal in these first three cases, indicating that the renal calcification was not of a metastatic nature resulting from secondary hyperparathyroidism. It would appear likely that, as in case 1, a high calcium intake in combination with the degenerative and inflammatory lesions of chronic glomerulonephritis provided the background for the nephrocalcinosis in cases 2 and 3.

Case 4 for many years followed a very puzzling and complex clinical course, exhibiting characteristics of both primary and secondary hyperparathyroidism, and this case probably should be set apart from the other three. The clinical evidence for chronic glomerulonephritis in this patient was not clear-cut, but at autopsy there was definite microscopic evidence of this disease. The renal calcification microscopically was present in the tubules of both cortex and medulla, in contrast to the other cases, but somewhat more so in the cortex. This differential distribution, however, was

not marked enough to be apparent on the x-ray films. In addition, it would seem likely that the unusual and extensive capsular and subcapsular calcification seen only in case 4 helped to mask the cortical predominance of the calcinosis in the renal films. Other differences also can be pointed out between the last case and the three preceding ones. Case 4 was the only one who showed definitely abnormal serum calcium and phosphorus values and who had secondary hyperparathyroidism. For this reason his kidneys could have been the site of metastatic calcification, a factor not existing in the other cases. Indeed, the medullary calcification in case 4 does suggest a metastatic type of calcification, such as was present in the lungs, while the coexistent cortical tubular calcification could have been of the dystrophic variety, as

FIG. 7. Roentgenogram of kidneys. Patient is a 15 year old boy with hyperchloremic acidosis. The nephrocalcinosis predominantly involves the regions of the medullary pyramids, while the cortices are spared. This calcium distribution is in striking contrast to that seen in figures 1, 3 and 4, and is also different in pattern from that in figure 5. Further clinical details of this case will be reported separately by one of us (W. R. C.).

was probably the case with the other three patients. Furthermore, the etiology of the systemic crystallinosis and the granulomata in case 4 still remains unsolved in spite of tissue analyses and a careful review of the history for medications that might explain the bizarre picture. This latter undiagnosed process, in addition to the proved glomerulonephritis, might have had some relation to the etiology and pattern of the renal calcinosis in the last case. Also of interest is the fact that in this case alone no history of excessive milk or alkali intake could be obtained. It is thus apparent from case 4 that not all instances of glomerulonephritis associated with nephrocalcinosis present the roentgen findings noted in cases 1, 2, and 3, but on the other hand one must keep in mind that the exceptional case in question was not a pure example of chronic glomerulonephritis.

While only a relatively few instances of nephrocalcinosis associated with chronic glomerulonephritis have been described, it is our feeling that the x-ray findings are characteristic enough that this type of nephrocalcinosis may be distinguished from the other conditions associated with renal calcification (table 1). To the best of our knowledge, chronic glomerulonephritis is the sole disorder, as yet, which has been associated with nephrocalcinosis strikingly predominant in the renal cortex as seen by x-ray examination. Calcification of the renal parenchyma primarily involving the cortex is so rare that one should strongly suspect underlying chronic glomerulonephritis whenever this pattern of nephrocalcinosis is observed. The great majority of cases of nephrocalcinosis, however, are associated with medullary rather than cortical calcification, and this distribution pattern also is distinctive by x-ray but is common to several disorders. Thus, the nephrocalcinosis associated with hyperparathyroidism, hyperchloremic acidosis, hypervitaminosis D and sarcoidosis typically consists of irregular coalescent rounded foci of calcification varying in size and occurring in the regions of the medullary pyramids. Occasionally the calcification appears wedge-shaped, conforming to the anatomic outline of the renal pyramids. Figure 7 demonstrates a typical example of medullary calcification in a case of hyperchloremic acidosis, which one of us (W. R. C.) has observed, for comparison with the cortical calcification of chronic glomerulonephritis. It would seem that those conditions characterized by medullary calcification are mostly associated with hypercalciuria alone in the absence of underlying renal tubular damage, with the possible exception of hypervitaminosis D, which is probably associated with degenerative tubular changes. The medullary distribution of the calcium would appear to be related to its higher concentration and precipitation in the collecting tubules. This serves to contrast with the combination of an inflammatory and degenerative cortical process and increased calcium intake producing cortical calcification in the cases of chronic glomerulonephritis we have just described.*

Summary

Four unusual cases of nephrocalcinosis have been presented, all associated with chronic glomerulonephritis. In three of these cases the calcification seen in x-ray films was confined mostly to the renal cortex and resulted in a striking roentgenographic picture, while in the fourth patient the calcification seen by x-ray was diffusely distributed throughout the entire kidney, although it was mostly in the cortex on histologic examination. This latter case (case 4), however, exhibited clinical and pathologic findings in addition

* One possible exception to this classification is a complex case we have observed of breast cancer with widespread bone metastases, in which one might have predicted a medullary rather than a cortical type of renal calcinosis. While no premortem x-rays of the kidneys were taken, postmortem films and histologic studies revealed predominantly cortical tubular calcification. This ovariectomized, adrenalectomized patient, treated variously with cortisone and testosterone, had proved hypercalcemia and hypercalciuria. There was no histologic evidence of renal disease; nevertheless, the kidneys showed nephrocalcinosis of a cortical type.

to chronic glomerulonephritis which set it apart from the other three cases and may have explained its differing x-ray appearance. In three of our four cases, as in the two cases previously reported, there was a history of excessive calcium ingestion which may have provided an additional etiologic factor in the calcification process. Nephrocalcinosis involving mainly the renal cortex strongly suggests an underlying chronic glomerulonephritis, since we have noted no other disorder which is associated with this roentgen pattern of renal calcification.

By contrast with chronic glomerulonephritis, other disorders associated with nephrocalcinosis—such as hyperparathyroidism, hyperchloremic acidosis, vitamin D intoxication and sarcoidosis, all of which have in common increased calcium excretion in the urine—result in calcium deposition which by x-ray examination is more marked in the medullary pyramids. This distribution also results in a strikingly typical roentgenographic picture.

ACKNOWLEDGMENT

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THYMOMA: DIAGNOSIS AND TREATMENT *

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THE diagnosis of thymoma can present much difficulty because of the unusual location, slow growth and lack of classic signs and symptoms.

The thymus usually undergoes gradual regression at adolescence but may persist beyond puberty and produce no symptoms. When the thymus does not regress it may compress mediastinal structures, undergo malignant change or give rise to myasthenia gravis.

Weigert [1] in 1901 first reported a case of myasthenia gravis associated with a thymoma. Since then, many reports confirming Weigert's findings have appeared in the medical literature. Seybold et al.[2] have found that 75.6% of their patients with myasthenia gravis had an enlargement of the thymus, and 15% of patients with thymomas had myasthenia gravis.

Harris,[3] Ambrosini,[4] Jones [5] and Janeway [6] described the most frequent clinical symptoms due to thymoma. Enlargement of the thymus, by virtue of its location, may produce compression of the mediastinal structures, resulting in cough, hoarseness, cyanosis, engorgement of neck veins and edema of the face and upper extremities. The most common complications are pleural or pericardial effusions, obstruction of the trachea and esophagus, or pulmonary invasion. Frequently, however, it gives no symptoms and may be found only on a routine chest roentgenogram.

The diagnosis of thymoma is suggested by an adequate history and the finding of a widened mediastinum on percussion, but the chest roentgenogram is of utmost diagnostic importance.

Any round, sharply defined mass situated behind the sternum and above the pericardial sac, found on a routine chest x-ray, is suggestive of a thymoma. Good [7] has shown that in some cases of myasthenia gravis the anteroposterior roentgenogram failed to reveal a thymoma which could be visualized on a subsequent lateral roentgenogram. The tumor may be found not only in its usual location, retrosternally, but also at the level of the ninth or tenth thoracic vertebra, above the diaphragm, in front of the pericardium, or on the anterior surface of the left main stem bronchus, as reported by Castleman and Norris.[8] Calcifications within the tumor were found in 13 of 45 cases described by Seybold et al.; the calcium was deposited peripherally in most tumors, but may be found throughout on occasion.

Grandhomme [9] in 1900 was first to introduce the term "thymoma" for any malignant tumor arising in the thymus gland. At the present time any

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tumor of the thymus, benign or malignant, is called a thymoma. The thymus may undergo carcinomatous or sarcomatous changes and may subsequently invade the surrounding organs, or produce distant metastases. According to Crosby,[10] this malignant tumor invades the lungs, pleura, mediastinal lymph nodes, heart, pericardium, trachea, vena cava and liver in order of frequency.

The following case reports exemplify the difficulty in making the diagnosis of thymoma.

Case Reports

Case 1. A 25 year old colored merchant seaman, admitted on October 13, 1952, had developed a "cold" about seven months prior to admission which persisted as a cough productive of small amounts of white sputum, and generalized chest aching. In the last two months dyspnea had occurred and had become progressively worse. In the week before admission the patient had noted the onset of hoarseness. He complained of considerable weakness and sweats, but had no chills or fever. His appetite was good, but he had lost 13 pounds in weight. He denied hemoptysis.

Fig. 1 A. *Case 1.* Admission x-ray, October 1952.

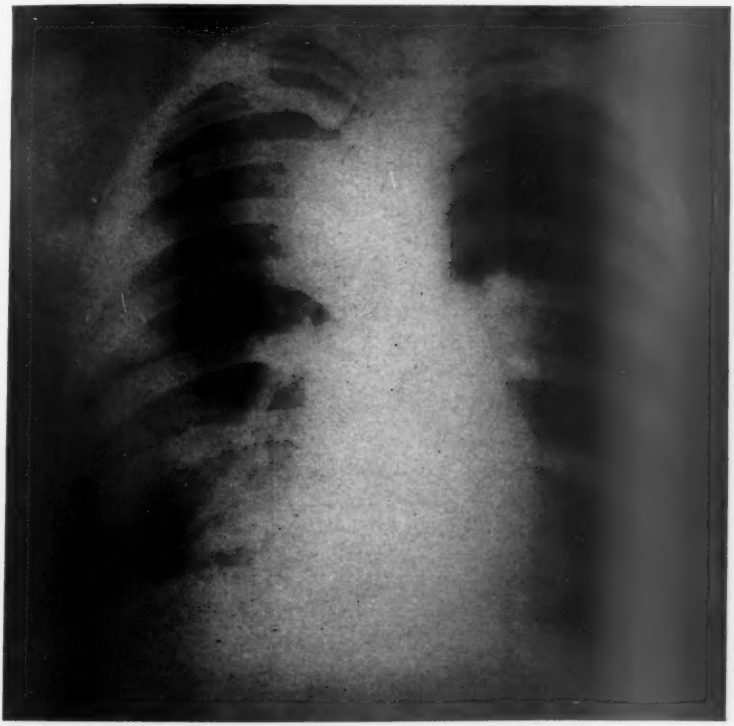

FIG. 1 B. *Case 1.* Photofluorograph, February 1952.

Past history revealed that he had had "pleurisy" 10 years previously, following which he noticed an increase in frequency of "colds." Family history revealed that the patient's father had died of pulmonary tuberculosis.

Physical examination revealed a thin, well developed male of 25 years, appearing chronically ill but not in acute distress. Temperature, 98.6° F.; pulse, 100; respirations, 24; blood pressure, 110/70 mm. of Hg. The pertinent positive physical findings were limited to the chest. Diminished tactile fremitus and dullness to percussion were noted over the left lower lung field posteriorly and laterally. The breath sounds were diminished over the same area, and fine inspiratory crackling râles which did not clear on coughing were heard over the remainder of the lung fields.

Laboratory Examination: The chest roentgenogram revealed several areas of ill defined, homogeneous infiltrations scattered throughout both lung fields. There was no widening of the mediastinum, and the heart size was within normal limits.

Urinalysis was normal; hemoglobin, 13 gm.; hematocrit, 44%; total white cell count, 7,050/cu. mm., with a normal differential. Sedimentation rate was 12 mm./hour (Cutler method); cephalin flocculation, 3 plus; thymol turbidity, 8.8 units; total protein, 10.5 gm.%, with 6.4 gm.% of globulin; serum calcium, 10.5 mg.%; inorganic phosphorus, 2.6 mg.%. Sputums were negative for acid-fast bacilli and

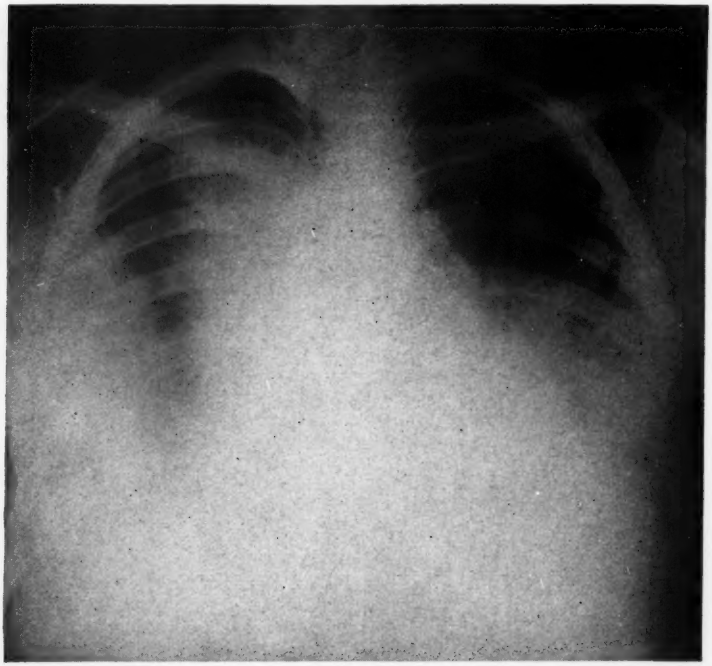

FIG. 1 C. *Case 1.* Posteroanterior x-ray, February 1953.

fungi on smear and culture. Blood serology was negative. Repeated second test strength PPD tuberculin skin tests were negative. The electrocardiogram and liver biopsy were within normal limits.

Hospital Course: In view of the patient's chest films, high serum globulin, negative PPD skin tests and racial origin, a presumptive diagnosis of sarcoidosis was made. This impression was substantiated by a routine photofluorograph, 5 by 7 inches, taken eight months prior to admission, which revealed pulmonary infiltrations similar to those noted on admission. Because of the development of increased dyspnea five weeks after admission the patient was treated with intravenous ACTH and then placed on oral cortisone. Initially, considerable improvement was noted without x-ray clearing. However, in two months dyspnea recurred and subsequently a left pleural effusion developed. Thoracentesis yielded 750 c.c. of straw-colored fluid, with a specific gravity of 1.032, 9 gm.% protein and 35,000 cells/cu. mm., predominantly lymphocytes. Weekly thoracenteses were subsequently necessary for the relief of dyspnea. A febrile period developed, unresponsive to penicillin. Streptomycin and isoniazid were then started because of the known increased incidence of tuberculosis in patients with sarcoidosis, and especially since steroid therapy was being given. Within three days the temperature returned to normal.

Repeated tuberculin test was negative; the x-rays of the long bones, hands and feet were normal. Total serum protein was 11 gm.%, with 8 gm.% of globulin.

The patient followed a progressively downward course, complicated by the development of cor pulmonale. He died on April 8, 1953, six months after admission.

Postmortem examination revealed a clear amber fluid in both pleural cavities (2,500 c.c. in the right, 1,000 c.c. in the left). The anterior superior mediastinum was increased to a width of 5 cm. by tumor tissue which extended over the mediastinum, especially on the left side and over the diaphragmatic leaves. Polypoid lesions composed of similar material were present in both pleural cavities, especially on the left side. These lesions were attached by short, narrow, relatively avascular stalks.

Practically all lung parenchyma was replaced by large nodules, measuring up to 12 cm. in diameter, which on section were pinkish gray in color. The left upper lobe bronchus was diffusely infiltrated by similar tumor tissue. The mediastinal lymph nodes were enlarged and tumor tissue was found along the great vessels up to the neck. The only other positive finding was a right ventricular hypertrophy.

Microscopic examination confirmed the diagnosis of malignant thymoma.

Case 2. A 49 year old colored American seaman was first admitted on August 8, 1951, because of a positive serologic test for syphilis which persisted despite seemingly adequate antiluetic treatment given in 1945, 1946, 1947 and 1951.

On this admission a routine chest film revealed an anterior mediastinal mass projecting off the right cardiac border at the level of the root of the aorta. The heart was normal, and no cardiac murmurs were present. Fluoroscopically, this

FIG. 2 A. *Case 2.* Posteroanterior x-ray of chest, 1948.

mass was believed to be an aneurysm of the ascending aorta. The patient was discharged to return for follow-up roentgenograms of the chest.

In June, 1952, the patient was re-admitted for reëvaluation. He had been completely asymptomatic. His serology continued positive. In May, 1952, he had received another course of penicillin therapy for "latent" syphilis. Repeat x-ray of the chest showed progression in size of the mediastinal mass, which now appeared to have a lobulated border. On this admission all laboratory studies, including electrocardiogram, ballistocardiogram and fluoroscopy of a swallow of barium, were within normal limits. It was believed this was an aneurysm of the sinus of Valsalva. The patient was again discharged.

The last admission to the hospital was on April 20, 1953. As an outpatient he had had serial x-rays which revealed continued progression in the size of the mediastinal mass, with no change in contour of the heart and great vessels. An angiocardiogram was therefore done, which proved that the mass was not an aneurysm but a distinct anterior mediastinal tumor.

Physical examination on admission was completely within normal limits.

Laboratory work-up included the following: red blood count, 4.5 million/cu. mm.; hemoglobin, 14 gm.; hematocrit, 44%; platelets, 330,000; white cell count, 7,300 with a normal differential. Urine was normal. Sedimentation rate (Cutler method) was 18 mm./hr.; prothrombin time, 75% of normal; Mazzini, 3 plus; Kahn, 2 plus. Electrocardiogram was normal.

At thoracotomy on April 23 a 6 by 4 inch reddish gray lobulated tumor was observed. It was situated at the right of the base of the heart and was covered by

FIG. 2 B. *Case 2.* X-ray taken in 1950.

FIG. 2C. *Case 2.* Pre-operative x-ray, 1953.

normal pleura. The tumor was believed to be completely removed. On cut section it showed several cystic areas, but for the most part was composed of gray tissue which was somewhat granular and friable. The microscopic appearance was described as that of a thymoma.

The patient's postoperative course was uneventful. He was discharged on May 12, 1953. As an outpatient he received a course of irradiation because it was felt that some thymic tissue might have been left in the thoracic cavity. He returned to full duty, and repeat x-ray of the chest revealed no recurrence.

This case emphasizes both the slow growth of these tumors and the fact that they may attain a rather large size without producing symptoms. It also points out the importance of angiocardiography in excluding a clinical impression of aneurysm.

Case 3. A 41 year old Puerto Rican seaman was admitted to the hospital for the first time on November 9, 1953, for investigation of an asymptomatic mediastinal mass found on routine chest x-ray. The patient had had routine employment chest x-rays every six months for 12 years preceding admission, but no evidence of a mass had been seen prior to August, 1953. It had apparently developed rather rapidly.

It is significant that the patient had no symptoms whatsoever referable to the chest. His general health was excellent and he had had no weight loss.

Past history and review of symptoms were noncontributory. Physical examination on admission was found to be completely within normal limits. The blood pressure was 130/90 mm. of Hg, the pulse 72; the cardiovascular system was essentially normal. Fluoroscopy revealed a nonpulsating, slightly lobulated mass just to the right of the base of the heart. Chest x-ray confirmed this location, and lateral views placed it in the anterior mediastinum. The electrocardiogram was normal. The remainder of the laboratory tests were within normal limits. Bronchoscopy disclosed an essentially normal tracheobronchial tree.

On November 23 a right thoracotomy was performed. A mass measuring 3 by 4 by 4 inches in size was found anteriorly at the base of the heart projecting into the right pleural space. It was covered by a layer of intact pleura which stripped easily from the tumor. The mass was densely adherent to the pericardium in places, but at no point was invasion noted. The main vascular pedicle appeared to come from the internal mammary vessels, although several venous tributaries to the innominate vein were observed. The entire tumor was removed. Chest suction was applied for 48 hours, and convalescence was essentially uneventful. On cut section

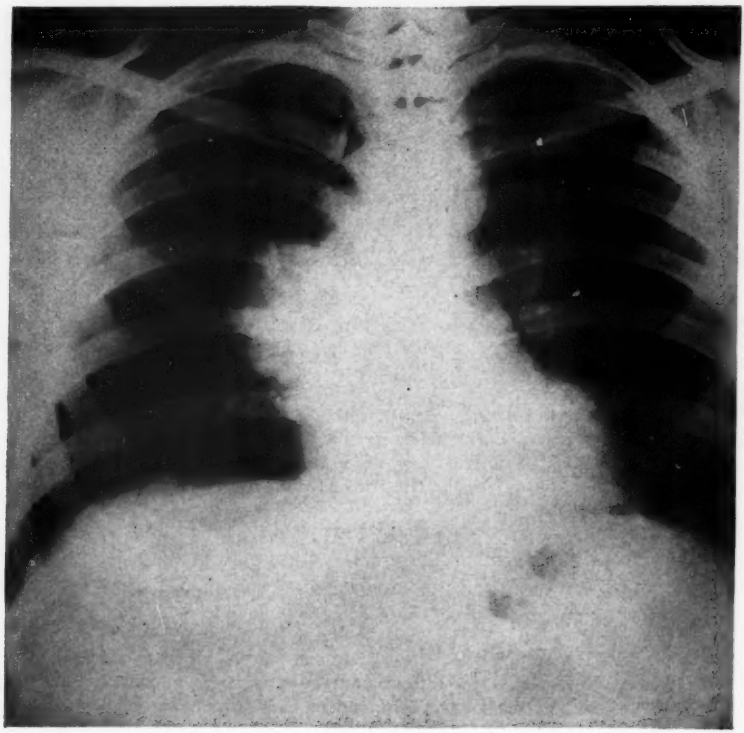

FIG. 3 A. *Case 3.* Admission x-ray, October 1953.

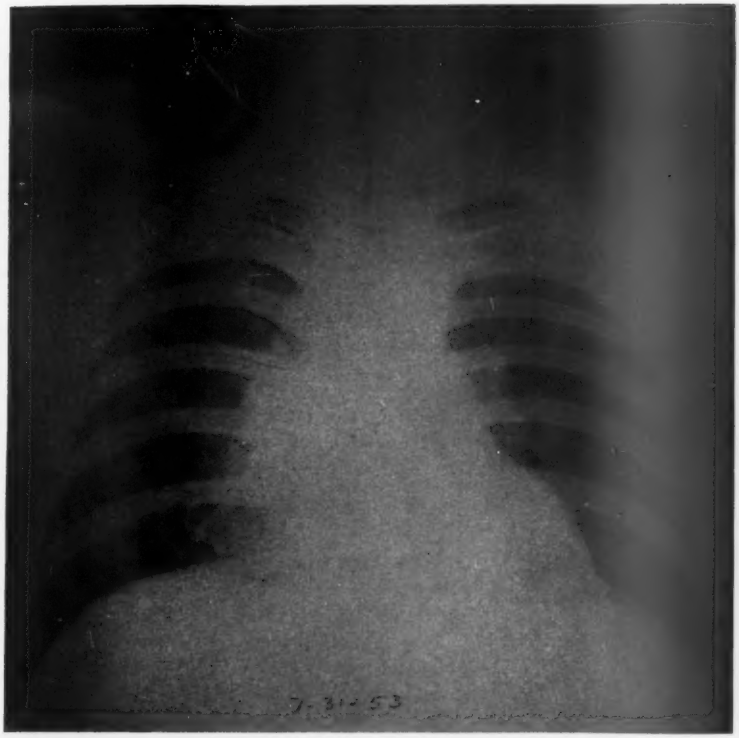

FIG. 3 B. *Case 3.* Routine x-ray, July 1953.

the tumor was noted to have a fibrous capsule; it was of a homogeneous dark red color and contained several cystic areas filled with dark bloody fluid. Microscopic sections were reported as showing "compact masses of tumor cells separated by fibrous bands containing vascular channels. Focally there are areas of intimate relationship between tumor cells and endothelial layer. Foci of lymphoid tissue are evident also exhibiting tumor masses. Definite capsular vascular wall invasion is noted. Infrequent mitoses are evident. Diagnosis: Angio-endothelioma, mediastinum, probably malignant." The microscopic picture was reviewed by consulting pathologists, each of whom felt the tumor was probably malignant but disagreed on the type of tumor. In our opinion it was most likely a thymoma with early malignant changes.

The patient was given a total of 4,000 r irradiation to the anterior mediastinal area. He was discharged and has returned to duty.

This patient's tumor was in many respects similar to that of case 2, but here the highly malignant potentialities of thymoma are shown. For this reason, early thoracotomy and resection are recommended.

Case 4. A 54 year old American seaman was admitted to this hospital on January 9, 1951, with a complaint of "pressure in the left chest" of approximately six months' duration. In June, 1950, the patient had noted the onset of sudden left chest pain aggravated on breathing, cough, fever and weight loss; this condition responded to penicillin therapy. A roentgenogram of the chest at that time revealed a bilateral pleural effusion. As a residual of this episode the patient had some dyspnea. In December, 1950, a recurrence of the left chest pain, pleural effusion and fever were noted, and the patient was again hospitalized in Germany and treated successfully with Aureomycin and penicillin. X-rays of the chest disclosed an anterior mediastinal tumor, and the patient was transferred to this hospital for further diagnostic studies and definitive treatment.

On admission the physical examination revealed considerable exertional dyspnea, and normal temperature and blood pressure. Several small shotty cervical lymph nodes were present. Chest examination revealed decreased breath sounds, dullness to percussion, and increased vocal fremitus in the right base posteriorly. Scattered râles were heard in the left base. Cardiac examination was normal. There were slight clubbing and cyanosis of the fingers.

Laboratory studies included a chest x-ray which revealed a right pleural effusion and an anterior mediastinal tumor mass. Chest x-rays obtained from the patient's employer which had been taken two years prior to admission revealed a similar tumor mass. The pleural fluid was clear and was negative for organisms and tumor cells. Urine, blood, sputum examinations and liver function studies were essentially normal. An electrocardiogram showed evidence of a bundle branch block. Biopsy

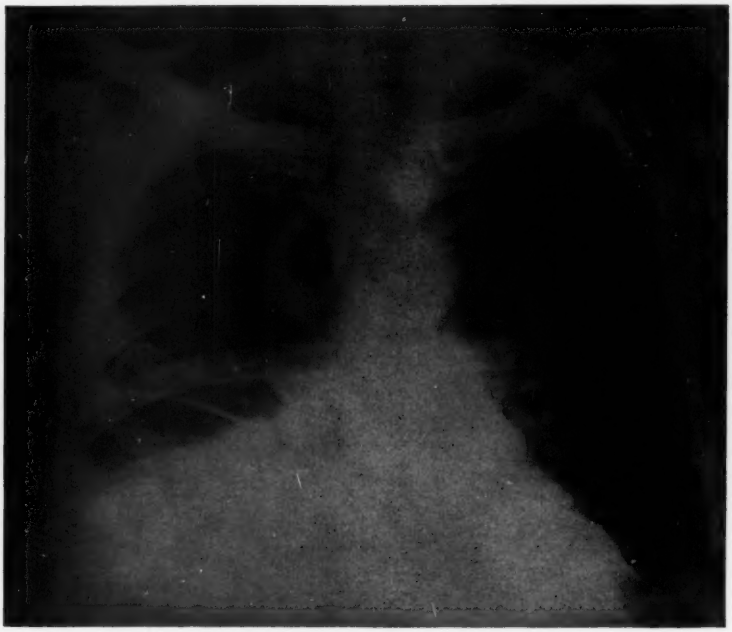

FIG. 4 A. *Case 4.* Admission x-ray, 1951.

FIG. 4 B. *Case 4.* Lateral x-ray, 1951.

of the cervical nodes revealed hyperplasia. Bronchoscopy on January 18, 1951, disclosed some external compression of both lower lobe bronchi, but no intraluminal tumor was seen.

Because of the marked dyspnea, and despite the clinical impression of inoperability, palliative surgery was recommended for the relief of symptoms.

At thoracotomy, on February 8, 1951, a pear-shaped pedunculated tumor mass was noted projecting from the anterior mediastinum into the right lower chest. It appeared to be encapsulated and showed no evidence of invasion. It was completely removed. The postoperative course was benign. Histologic examination of the specimen revealed a benign thymoma. This patient received no x-ray therapy and

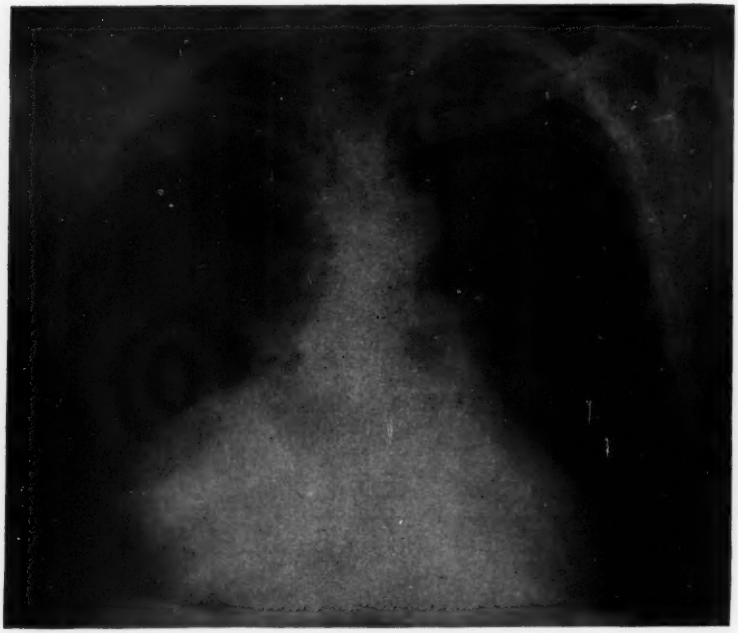

FIG. 4 C. *Case 4.* Last pre-employment x-ray, 1949.

returned to duty. Follow-up chest x-rays 18 months later revealed no recurrence of the tumor.

This case represents one in which compression of the tracheobronchial tree resulted in distal pneumonitis with intermittent pleural effusion. Clinically the lesion seemed to be inoperable, and yet at surgery the tumor was disclosed to be noninvasive and readily resectable.

DISCUSSION

Mass chest x-ray surveys and many routine preëmployment roentgenograms reveal tumors of the chest in patients who have no clinical manifestations.

The finding of an anterior mediastinal mass warrants a careful and complete work-up in an attempt to establish a diagnosis. This includes lateral and oblique chest x-rays, careful fluoroscopy with barium swallow bronchoscopy, hematologic studies and a cardiovascular survey. Angiocardiography may be necessary to establish the position of the mass in relation to the heart and great vessels. If the diagnosis of anterior mediastinal tumor is made, or if there is reasonable doubt as to the exact etiology of the

mass, the indication for exploratory thoracotomy with removal of the tumor exists.

For surgery, general endotracheal anesthesia is preferred, since one or both pleural spaces may be entered. Exposure is adequate using the lateral recumbent position, but more recently the median sternotomy incision has been shown to provide excellent visualization of the thymic area. Unless actual invasion of surrounding vital structures has occurred, these tumors are usually relatively easy to remove. The numerous vascular attachments require precise hemostasis. Suction drainage of the entered pleura is of aid in prompt reëxpansion of the lung, and the usual close postoperative observation is required to prevent atelectasis, pleural effusion pockets and hemothorax. The patients are usually ambulant by the fifth day postoperatively. Morbidity and mortality in the uncomplicated case are very low, but if invasion of neighboring structures has occurred, increased risks are assumed in the attempt to extirpate the tumor completely. These risks are justifiable, since no other successful method of curing these tumors is yet apparent.

It cannot be emphasized too strongly that the finding of tumors in the anterior mediastinum demands immediate thorough investigation, with recourse to exploratory thoracotomy at an early date if other diagnostic procedures are unavailing.

Summary

Thymomas may be asymptomatic and be found on routine chest roentgenograms, or they may be symptomatic and give rise to manifestations due to compression of mediastinal structures. Myasthenia gravis may be another manifestation in 15% of the cases.

The cases presented above stress the difficulty in making the diagnosis of thymoma and the advisability of early thoracotomy.

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PATTERNS OF PROTEIN EXCRETION BY THE KIDNEYS *

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Introduction

The frequency of casual, intermittent and orthostatic proteinuria ("albuminuria") is well recognized. Because of usually limited opportunity for study and disconcertingly variable results upon repeated urine examinations, serious effort is seldom made to distinguish between known varieties of inconstant proteinurias. The term "benign proteinuria" has been adopted as a blanket diagnosis for all instances of proteinuria not clearly related to organic renal disease. The exceedingly common miscellaneous transitory or accidental proteinurias apparently following a myriad of temporary and insignificant renal and nonrenal disturbances as well as laboratory error are rarely repetitive and are indeed benign. Orthostatic or postural proteinuria, which is also quite common, has been clearly defined by competent observers as characterized by regular excretion of protein in the urine upon sudden change from prolonged rest to the erect posture. If casual or unsuitable specimens are examined, protein excretion in such instances may appear to be intermittent. Despite adequate evidence in the literature to the contrary,[3, 4, 5, 11, 31] it is usually stated that orthostatic proteinuria is a transient phenomenon of youth which disappears and is without further significance except for the confusion it causes. It is rather surprising that a very common disorder with evidence of chronic (persistent) degenerative renal lesions, as indicated by regularly repetitive proteinuria and sediment abnormalities (Addis), has been quite casually accepted as insignificant and benign on relatively trivial and unimpressive evidence.

A review of the available literature shows that what has been indicated in the relatively few cases of orthostatic proteinuria followed for any time is that protein excretion apparently continues indefinitely and that such patients do not develop renal insufficiency rapidly. In few instances indeed has there been any clear-cut proof that follow-up studies have been confined to true orthostatic proteinuria. As will be shown, orthostatic proteinuria in itself is a deceptive term in the implication that it represents a discrete clinical or pathologic entity.

The unreliability of single or even multiple casual urines in detecting orthostatic proteinuria, a process usually limited to short periods of the day, is apparent. Without reliable means of study, many cases escape detection

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entirely. Without a base line or point of reference, follow-up studies can yield only limited information. A conditioned urinary protein excretion test previously described [1, 6] has been applied to the study of approximately 4,000 individuals with proteinuria. As previously reported, protein excretion patterns obtained by this test have been found individually consistent and well correlated with clinical and other laboratory findings for the type and severity of the renal disorder. These patterns have been used as a base line to determine persistence of protein excretion (chronicity) and to detect progression.

Accumulated clinical and laboratory data on these and other patients together with physiologic studies are planned to appear as subsequent individual communications in developing a tentative composite picture of these obscure forms of proteinuria. From such observations, and from other sources, evidence will be reviewed in this report suggesting that orthostatic proteinuria is associated with a variety of renal disorders which are usually chronic and persistent and are often progressive. By prior selection and definition such cases usually represent chronic latent renal disorders of relatively slow progression.

Pathologic Physiology of Protein Excretion by the Kidneys

Protein excretion by the kidneys involves many complex physiologic alterations, many of unknown nature. Only a few more recent advances pertinent to this phase of renal physiology will be reviewed. For details, reference is made to original authoritative sources.[7, 8] The serum proteins apparently enter the glomerular filtrate in a nonspecific manner, as do other biologic filtrates (cerebrospinal, edema and ocular fluid).[9] Their filtrate concentration is estimated at between 20 and 30 mg.%. Some renal physiologists have drawn a fine distinction between glomerular filtration of water and diffusion of dissolved substances through the glomerular membrane. Filtration of fluid is governed by the capillary hydrostatic pressure and opposing osmotic pressure of the plasma proteins within a semipermeable membrane. Dissolved substances and (apparently to a limited degree) proteins follow laws of molecular diffusion, influenced by concentration gradients and diffusion through capillary membranes (permeability). The concept of uniform pores in the capillary walls is questioned, and evidence has been presented suggesting that the membrane may be a gelatinous syncytial structure with fibers and spaces of molecular dimensions.[8]

Complex mechanisms regulating intrarenal pressure adjustments have been investigated by Winton, Swan and others.[8] The kidneys appear capable of withstanding moderate elevations in arterial, venous and ureteral pressure. Little alteration in blood flow was observed following experimentally induced increase in renal arterial pressure. Winton does not consider this resistance as being entirely explained by automatic arteriolar vasoconstriction. Moderate increase in ureteral pressure exerted little effect

upon arterial flow. Moderate elevation in renal vein pressure to about 20 mm. of mercury caused little change in renal blood flow and renal functions. These observations tend to confirm previous theoretic deductions by Gomez.[10] Apparently only marked increase in venous pressure can overcome these intrarenal regulating mechanisms.

There has been no essential change in concept concerning the rôle of the tubules in protein reabsorption. With filtrate concentration of 20 mg.%, 40 gm. of protein are reabsorbed daily.[11] The process of protein reabsorption or transport involves intracellular enzymatic processes, and may be considered tubular digestion of protein. This function may be subject to strain or exhaustion by excessive or prolonged load.[9, 11] Under any conditions urinary protein excretion represents the cumulative opposing effects of glomerular filtration and tubular reabsorption. Proteinuria is usually due to increased glomerular protein filtration, which is frequently accompanied by actual or relative tubular protein reabsorptive impairment. Protein excretion in nephritis has been directly related to the glomerular filtration rate.[7] Congo red and T1824, dyes of high molecular weight, are excreted in direct proportion to albumin.[8, 12] Similar inferences are drawn by Bradley [13] with PVP. Increased protein filtration occurs with active glomerular lesions (increased permeability), and follows elevated serum albumin concentration [14, 15] (increased gradient), and small or abnormal serum proteins (myeloma, etc.).[12] Proteinuria is rarely marked in acute nephritis when capillary damage is most intense. The greatest protein excretion occurs in nephrosis, when glomerular lesions are minimal and changes are most conspicuous in the renal tubules.

The glomerular circulation presents an enormous surface area for potential loss of serum proteins, with the tubules furnishing a secondary line of defense to prevent or limit this process. Breakdown of the tubular barrier is followed by marked urinary protein loss. With tubular overloading the filtrate protein concentration and viscosity rise. Oliver [16] considers increased viscosity of the glomerular filtrate capable of slowing its flow and favoring coagulation of protein as casts, with lumen obstruction and distortion of renal architecture. Bence Jones proteinuria is known to produce tubular blocking through large casts. Proteinuria of short duration is not believed to damage the kidneys, but, if prolonged, this eventuality is very probable. Lippman found tubular obstruction by casts with experimental proteinuria in rats, and reported distinct parallelism between protein excretion, casts and epithelial cells in man.[9]

Hyaline casts in particular are believed to be due to protein precipitation within the tubule. Excretion of both albumin and globulin following continued Bence Jones proteinuria and after infusion of albumin [14, 15] is considered due to tubular saturation. Increased urinary globulin usually occurs in conditions with severe glomerular damage or impaired renal function.[12, 17] Blackman [18] considered precipitation of globulin in the filtrate as contributing to glomerular hyalinization in nephritis.

The exact mechanism and significance of renin proteinuria are still obscure. It appears to result from both increased glomerular filtration and diminished tubular reabsorption of protein.[19, 20, 21] Adrenalectomy abolished renin and spontaneous proteinuria in rats, which were then restored by cortisone and DOCA.[22] Angiotonin also produces experimental proteinuria.[22] Concurrent pressor effects and proteinuria after renin were considered by Addis to indicate efferent arteriolar vasoconstriction similar to that in the adrenalin proteinuria described by Starr.[23] In more recent observations, Rather found no relation between experimental hypertension in rats and occurrence of proteinuria.[24]

In three-quarter nephrectomized animals the immediate loss of renal tissue causes a little proteinuria which increases progressively. Adrenalectomy is without effect in these cases. Over a period of months glomerular lesions with basement membrane thickening and proliferative changes similar to those of lipoid nephrosis develop.[22] It is implied that glomerular as well as tubular lesions result from continued proteinuria. Rather also points out that glomerular as well as tubular lesions are common in proteinuric rats.

Various circumstances accompanied by vasomotor reactions are described as producing transient proteinuria in man.[7] These include immersion of the body or extremities in cold water, unusual excitement and epinephrine. It has been assumed that urine protein follows renal vasoconstriction under conditions similar to those experimentally produced by Starr.[23] Chesley [25] reported immediate proteinuria with elevation of blood pressure after cold, both effects preceding changes in filtration rate. Odell [26] observed traces of protein in the urine of three cases who also developed marked antidiuresis during the cold pressor test. The occurrence of urinary protein in man under conditions of stress and emotional tension has been noted.[27, 28, 29]

Marked protein excretion follows renal vein thrombosis, and proteinuria in congestive cardiac failure has been ascribed to increased renal vein pressure. Bull,[30] modifying the lordotic theory of Jehle,[31] ascribed orthostatic proteinuria to increased inferior caval and renal vein pressure from a liver rotated in erect lordosis. The adaptability of the kidneys to moderate increase in renal vein pressure with minimal changes in dynamics has been discussed. It appears doubtful that the moderate elevations of renal vein pressure observed in congestive failure and reported by Bull can be accepted without further evidence as being capable of inducing proteinuria. Bradley and Bradley [32] found variable amounts of protein in the urine of normal subjects after abdominal pressure, but on most occasions this was not striking. Under identical conditions, these results have not been duplicated in our laboratory.

The body fluid balance assumes increasing importance in relation to urinary protein concentration and detection. With marked polyuria, even moderate amounts of protein may be diluted beyond detection. Spontaneous diuresis has been observed even under hydropenic conditions, with emotional

tension.[33, 34] Hinckle [34] observed diuresis during the early stages of total fasting.

Oliguria may be marked on standing, due to secretion of the antidiuretic hormone by the hypophysis. This effect is particularly marked if syncope is associated with the prolonged passive erect posture; and lordosis [7] urine rates per minute may fall as low as 0.25 c.c., or to 5% of the control supine rate.[30] Similar effects may follow painful stimuli, including cold immersion, exercise, smoking and alarm reactions. There has been recurrent speculation [36, 37] that extreme oliguria may cause apparent proteinuria through concentration of normally present urine proteins.

Material, Method and Application

Approximately 4,000 individuals, hospitalized because of proteinuria discovered on routine examination in the period 1950 to 1954, were studied, some on repeated occasions, by the conditioned urine protein excretion test. Results have been correlated with clinical and other laboratory findings. Cases referred for study were selected at military examining stations because of urinary protein in several specimens. It is estimated that about three quarters of cases with initial proteinuria were eliminated from this hospital study because of subsequently negative urine findings. It is not implied that this screening method is to be considered accurate. Some cases of orthostatic proteinuria probably were missed in one random urine examination, while others originally found positive may have been excluded erroneously. Nor can the relative incidence of protein excretion patterns found in this hospitalized group be considered generally representative, being heavily weighted by this method of selection for cases with marked orthostatic and continuous proteinuria.

All patients were studied under generally adequate ward conditions, which, however, fell far short of the metabolic type of supervision. Study of patients with continuous protein excretion in the last two years included accurate Addis counts, protein excretion rates and the usual clinical tests of renal function. Only Addis tests on specimens collected under required conditions and performed shortly after collection by trained personnel have been found to be of any value. Other additional procedures (limited by hospital facilities) included intravenous urography in approximately 150 cases, and occasional urologic study. The routine demands of this test upon ward personnel and laboratory were of the most simple and primitive nature. In a selected number of cases, studies of serum and urine proteins by electrophoretic methods and determinations of renal dynamics and function by clearance of inulin and PAH, and TmPAH and Tm glucose were made at the First Army Renal Research Laboratory.

Approximately 350 patients were rehospitalized at varying intervals to evaluate further their protein excretion patterns and clinical status. Follow-up cases were largely administratively selected, with a preponderance of

continuous and frequent proteinuria and irregular patterns. Correction for such bias will be made by controlled follow-up studies and by statistical methods. Recognition of these unavoidable limitations has necessarily limited conclusions at this time to qualitative form.

Methods

The need for a test to distinguish between variable, inconstant (orthostatic) and continuous proteinuria is obvious. Protein may be missed in random dilute urines and even in multiple or consecutive urine specimens unless they truly represent periods of rest and activity adjusted for lag between urinary secretion and collection. Failure to provide these conditions may explain variable experiences with less closely supervised serial urine tests. In general, satisfactory supervision of diet and fluid intake, of activity, and of specimen collections can be obtained only under hospital conditions, with trained, presumably diligent ward personnel. Only rarely can this procedure be left to the discretion or responsibility of the patient as an ambulatory procedure.

With minor modifications, the procedure previously reported has been followed.[1, 6] The test requires collection of two consecutive resting night and three day urine specimens following prescribed diet and activity. Fluid, salt and protein restrictions generally assure sufficient urine concentration. The first specimen is collected in the late afternoon on the day of hospital admission. After dinner the patient goes to bed and does not arise until the following morning. The specimen voided after two hours' rest is discarded by the attendant. The first night specimen is collected at 5 a.m., the patient voiding while in bed, and the second specimen approximately two hours later, immediately on his arising. The first two morning specimens are then collected when obtainable, the patient remaining ambulatory. Adequate information may be obtained from a four specimen test, with only one morning urine, but five specimens are more reliable. It has not proved practical to have patients assume the erect lordotic position, whether standing or kneeling, because of the frequency of syncope. Although some mild cases of orthostatic proteinuria not otherwise demonstrated may be missed, it is not believed that the accuracy of this test is vitiated by omission of this maneuver.

Interpretation: No validity is attached to protein-negative urine specimens of low specific gravity (below 1.018). Conversely, traces of protein in urine of small volume, insufficient for specific gravity, are viewed with suspicion. The two night resting specimens, collected under presumably identical conditions, should be similar, and any discrepancy suggests error or uncontrolled extraneous conditions. Any standard qualitative urinary albumin test, such as the 20% sulfosalicylic acid, is acceptable. Although microscopic examination of all fresh specimens is desirable, for practical purposes this may be limited to the night specimens and to all other speci-

mens positive for protein and blood. Benzidine or orthotoluidin tests for blood are performed routinely on all specimens. The initial night specimen, when accurately timed and preserved, may be used for the Addis count. Since hydropenic conditions have been maintained, this specimen also serves as a urinary concentration test.

Three simple standard "patterns" of distribution of urinary protein in those specimens are possible. Protein may be present in all urines (*constant pattern*), inconstantly present (*orthostatic pattern*), or completely absent (*negative pattern*). Discrepancy between the two night collections, or very rare instances of positive night and negative day specimens, is considered an irregular pattern and requires immediate repetition of the entire test. Irregular patterns have been found in most instances to be due to collection errors or arising at night. Some may be due to post-renal proteinuria, which follows chance distribution. Possible combinations or patterns of protein excretion are schematically presented in table 1.

TABLE 1
Urinary Protein Patterns
(Schematic)

Urine Specimen	A Constant	B Negative	C (Orthostatic)	D Irregular
1	+	−	±	±
2	+	−	−	− +
3	+	−	−	+ −
4	+	−	±	±
5	+	−	±	±

If any question arises, the test should be repeated before the patient leaves the hospital. By this means, uninterpretable results are avoided and irregular patterns limited. Irregular patterns are subdivided into two types most closely approximating the two standard forms. If opportunity for repeating the test is not possible, the irregular orthostatic (several valid day specimens negative for protein) may be considered orthostatic. This does not hold true for the irregular constant (all day specimens positive), which may prove either orthostatic or constant on repetition. The negative pattern is presumptive when one day specimen is not valid because of dilution. If several specimens are excessively dilute, the test is considered uninterpretable. The intent in general is to avoid reliance upon a single urine examination.

To clarify any ambiguity, the terminology is reviewed briefly. Over the 24 hour periods, proteinuria may be absent entirely (negative pattern), present in one or more specimens (orthostatic pattern), or remain continuous day and night (constant pattern). Irregular patterns are those with protein in one and not the other night specimen, or in both with negative day specimens. Studied over a longer period of days, proteinuria may disappear, may be present occasionally (intermittent), or may be present daily (per-

sistent), although not necessarily in all specimens of the patterns. Attention is called to slight change of terminology in the present report, the term "orthostatic" replacing "inconstant" as a pattern diagnosis.

Results

A. The Serial Urine Protein Excretion Test: The serial urine protein test has been employed in the study of approximately 4,000 patients over a four year period, with about 300 immediate repeat tests and approximately 350 repeat tests at varying intervals of up to three years. As previously noted, this investigation could not be planned or designed except in part, being largely collateral and secondary to the basic study of rapid evaluation, for military induction, of individuals with suspected renal disease. Pending statistical analysis of data and subsequent planned control studies, results will be presented in qualitative form. Minor modifications of the original method have been made to improve accuracy. (Some were frequently imposed by expediency.) The major source of error has come from the imperfect coöperation of patients and ward attendants in complying with the simple requirements of this test. Checks incorporated in the method have consistently exposed derelictions in ward collections or in laboratory technic. Improved results following correction of unsatisfactory conditions have been strong confirmatory evidence of the consistency of results which cannot be translated into mathematical form. In justice to local hospital personnel, it must be emphasized that the test was performed in a large ward in which other patients were being processed rapidly for many other diagnostic problems during periods of frequent change in staff. Under the most aggravated temporary conditions, irregular and uninterpretable tests together did not reach 10% and usually were considerably less. With reasonable supervision, including immediate repetition of the test as required, uninterpretable tests have been eliminated and irregular patterns reduced to 2%. It is probable that individual or group tests performed under constantly well controlled conditions would approximate these results.

Composite tables of relative incidence of various patterns for most of this period have been previously published.[8] They include past errors and artifacts that have been largely eliminated by repetition of the test; they do not reflect recent experiences. Figure 1*a* presents a distribution chart of various patterns with clinical equivalents in the hospitalized group. Figure 1*b* presents the estimated incidence of various patterns in the approximately 15,000 ambulatory subjects with initial proteinuria from whom this hospital group was derived. In deriving figure 1*b*, the conservative assumption has been made that few cases of constant proteinuria are missed initially or on repeat examinations. This may not be true if urines are excessively dilute. However, correction has been made for the manifestly large error in detection of orthostatic proteinuria in initial specimens and in repeat casual

specimens at examining stations. In either instance these estimates are considered conservative.

On immediate repetition of the hospital test, few significant variations in regular basic patterns were observed. The important constant pattern was almost invariably reduplicated (95%). Irregular patterns become regular in nearly all instances (97%). Although slight variations were obtained over the long term, negative and orthostatic patterns were quite consistent. In only a few instances did the orthostatic pattern progress into the constant over short periods. Clearing of constant and orthostatic patterns in part or entirely was observed in conditions associated with temporary hematuria or pyuria. Clinically, the constant pattern was observed in all instances of chronic nephritis as well as in cases with major congenital renal defects, advanced chronic pyelonephritis and occasionally in severe hypertension.

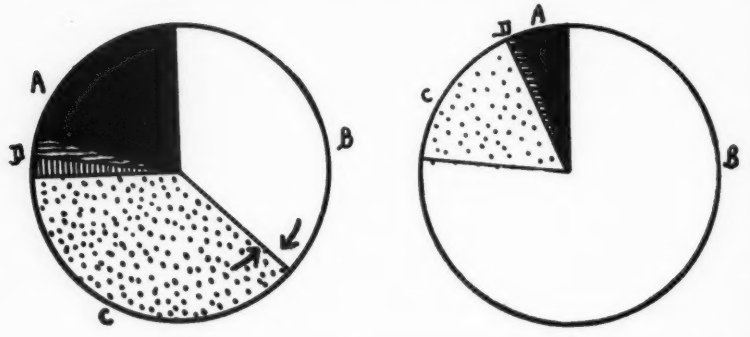

FIG. 1. *a*.—Relative incidence in 4,000 hospitalized individuals. *b*.—Estimated relative incidence in approximately 15,000 ambulatory individuals with proteinuria. A.—Constant pattern (continuous proteinuria). B.—Negative pattern. C.—Orthostatic (inconstant) pattern. D.—Irregular patterns.

The subjects examined being young and apparently well, other conditions were rarely encountered. However, a considerable number of patients with the constant pattern presented normal urinary sediment.

In approximately 35% of patients with recently documented proteinuria (in a minimum of two specimens), a negative pattern was obtained at subsequent hospital study, usually within an interval of one month. Initial proteinuria in these cases may have been due to laboratory error, to postrenal contamination, or to temporary disturbances (accidental) of a nonrepetitive nature. However, a number of such negative patterns again showed urinary protein subsequently; and a history of proteinuria in the past of a severity sufficient to cause rejection for military service was not infrequent in this group.

Results justify the following summary. Properly performed and interpreted, the conditioned urine protein excretion test offers an accurate and

practical method of differentiation of advanced renal disease, represented by continuous proteinuria (constant pattern), from the inconstant or orthostatic pattern. Inherent checks in the method expose laboratory or frequent collection errors. In conjunction with clinical and other laboratory observations, this procedure furnished a base line for further observations of obscure cases of proteinuria. Laboratory errors, inherent in casual and even multiple urine examinations, are greatly minimized because individual specimens serve as checks upon each other, being arranged to yield results which fall into several simple predictable patterns.

B. Clinical Observations—Orthostatic Proteinuria: No individual clinical picture can be derived that will describe suitably the clinical and laboratory findings and course of the obscure, inconstant proteinurias. Fleeting and unpredictable excretion of protein in the urine often is due not to renal disease but to physiologic disturbances and laboratory error. The present low estate of routine urine examinations requires little elaboration. Transient or accidental proteinuria may be due to postrenal disease or may follow stress conditions, especially cold, fright and other emotional stimuli. Circumstances causing proteinuria are often associated with mild syncope and antidiuresis. About one third of the hospitalized cases in this study with recent, documented proteinuria in several specimens gave completely negative protein excretion patterns. In the absence of history or other findings, such cases may be considered transient or accidental and without clinical significance.

Proteinuria may appear intermittently, demonstrable on some occasions and not on others. Often there is a strong implication of emotional instability, with easy tendency to syncope and sympathetic excitation, with sweating and evidence of neurocirculatory inadequacy. No clear-cut physical habitus is evident, but emotional and neurocirculatory factors are too striking to be readily dismissed. The term "orthostatic proteinuria" is purely descriptive for consistent or frequent excretion of protein in the urine following standing. It has no other specific meaning and is not confined to a single clinical or pathologic entity. Conditions associated with this finding may shed light on possible causes of this disorder, but a formal classification is not justified. A past history of nephritis or pyelonephritis was obtained in a small but probably significant number of instances. More impressive are the occasional instances in which this condition follows documented glomerulonephritis. Despite apparent derivation from previous glomerulonephritis (healed with defect), the urinary sediment (individual and Addis count) in such cases is completely normal. Orthostatic urinary protein excretion in older persons with hypertension and without a history of nephritis was interpreted in this study as a result of primary renal arteriolar disease. The converse may be the case. Hypertension and orthostatic-type proteinuria with normal sediment followed several instances of acute glomerulonephritis.

Because of practical obstacles, urography was obtained in only 56 cases

of patients with orthostatic proteinuria in this study. Renal abnormalities were reported in 18 cases, including four instances of bifid pelvis or ureters, and several with questionably low or displaced kidneys or poor filling function. Major renal abnormalities were demonstrated in 11 of the 56 cases. History of lumbar pain with hematuria or pyuria was usual in this last group.

The majority of cases with orthostatic proteinuria presented no abnormal history or unusual findings. Perhaps because of the youth of the individuals under survey, emotional and constitutional factors were conspicuous. In previous observations [29] the role of emotional stimuli was shown. Proteinuria developed in a large group of the intermittent variety following excitement, mild pain (venipuncture), cold, tilt and erect lordosis, all conditions associated with apprehension, discomfort and occasional syncope. Control normal individuals under identical conditions did not exhibit proteinuria.[29]

Gradations of severity of orthostatic proteinuria may be based on the diurnal distribution of proteinuria. In the intermittent form, protein may be completely absent some days. In others, protein may appear only for short periods during the day, while in some, most day urines are proteinuric. Finally, there are cases in which proteinuria is constantly present in all day specimens and absent only at night. Correlation between diurnal distribution and the severity of proteinuria evidenced by excretion rate has been observed.

There is no basis to warrant formal classification of orthostatic and other obscure proteinurias. They apparently result from a number of diverse pathologic conditions and functional disturbances. Various pathologic conditions are clinically demonstrable in some cases of orthostatic proteinuria. This subtype may be classified organic, in contradistinction to the majority of cases with no overt renal disease. In general, the more severe types of orthostatic proteinuria (constant diurnal) occur in association with organic renal disease. In diseases such as hypertension, diabetes, amyloidosis and collagen disease, inconstant (orthostatic) proteinuria is an incidental finding. In other instances, orthostatic proteinuria may be the sole presenting abnormality. Previous glomerulonephritis, coexisting congenital renal abnormalities, pyelonephritis or urologic disease may be discovered in such instances only after careful clinical and laboratory study. Postrenal proteinuria may be a variable, irregular and confusing differential requiring careful urologic investigation.

Persistency of Orthostatic Proteinuria: One hundred seventy cases of orthostatic proteinuria were reëxamined at intervals varying from several months up to three years (average, one year) by the controlled urinary protein excretion test. In 130 cases protein was found persistently in at least one day specimen of the pattern on repeated occasions. Including initial findings, protein was present in the urine in these 130 cases on at least three (usually more) occasions for the entire period of observation. In many

of these patients, a history of proteinuria as far back as 10 years was obtained. Due to the relatively short period of observation (average, one year), only a few instances of progression from severe diurnal orthostatic to continuous proteinuria have been observed, usually in cases with marked renal defects.

C. Clinical Observations: Obscure Continuous Proteinuria. Approximately 750 patients with continuous proteinuria were studied, of which one third were due to manifest active glomerulonephritis or pyelonephritis, as indicated by abnormal sediment. About 100 other patients eventually revealed urinary sediment abnormalities which justified inclusion in this same group. It is unnecessary to emphasize the difficulties of differentiating between chronic nephritis and pyelonephritis. In the long-standing variety, with quiescent infection after antibiotics, chronic pyelonephritis cannot be distinguished clinically from chronic glomerulonephritis.[12] In either condition, pyuria, hematuria, casts, hypertension and renal impairment may be present. In early or untreated pyelonephritis, pyuria and positive urine cultures may be of differential value, but proteinuria and sediment abnormalities are exceedingly variable. Renal infection often is superimposed upon major or minor congenital renal abnormalities. Not only can the differential diagnosis not be made with any degree of precision clinically, but also, as pointed out by Fishberg, it is often confused at postmortem examination. The few cases classified as pyelonephritis in previous tables were clear-cut, but many were undoubtedly included as glomerulonephritis.

In the remaining 400 patients with continuous proteinuria the urinary sediment and other routine laboratory and clinical findings contributed little to the differential diagnosis. These individuals were usually reëxamined as hospital patients several times before final rejection for military service. The great majority revealed minimal casts or no urinary sediment abnormalities in casual specimens and Addis counts. It may be possible, nevertheless, that these cases represent instances of latent chronic glomerulonephritis, with minimal sediment abnormalities unrecognized on repeated examination. It is equally possible that other, less frequently encountered diseases may have been included in the rubric of chronic glomerulonephritis (Fishberg). About 30% of these patients revealed elevation in blood pressure, but very few had extreme hypertension. Other systemic conditions which may produce renal disease of a severity sufficient to cause continuous proteinuria were lacking.

One hundred patients in the sediment normal group were studied by means of intravenous urography. As far as possible, selection of cases was avoided. Severe renal defects (usually congenital, but in several instances found to be traumatic) were detected in 24 instances, and minor abnormalities in 20. The significance of the latter is in doubt in view of the frequency of minor renal variation in normal people. Hypertension was particularly conspicuous in those with severe defects. Although no precise deductions are justified, the following conclusions may be permissible.

Severe congenital (or acquired) renal defects may account for an appreciable number of instances of continuous proteinuria in young individuals without history of renal disease and with apparently normal urinary sediment. Being usually unilateral, severe impairment of renal function with azotemia

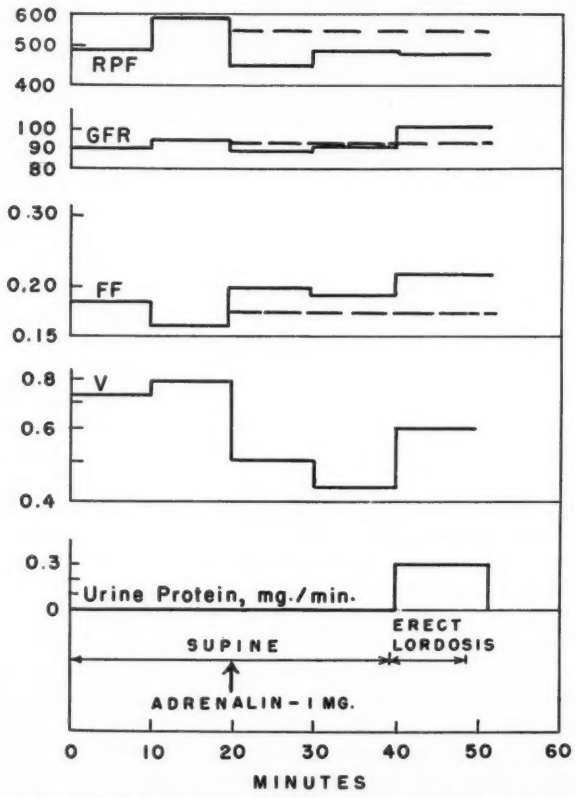

FIG. 2. The effect of subcutaneous epinephrine upon renal function and proteinuria in a case of orthostatic proteinuria. In the supine position, epinephrine produces a fall in renal plasma flow (clearance of PAH) and to a less extent in glomerular filtration (clearance of inulin) and diminution in urine volume. Proteinuria does not occur under these conditions, but promptly follows erect lordosis.

is rare, although hypertension is frequent and impairment of maximal urinary concentration may occur. The majority of instances of sediment-negative cases of continuous proteinuria remain unexplained. They may represent recovered or very latent cases of chronic glomerulonephritis (healed with defect), or perhaps may be due to other causes to be considered.

D. Physiologic Observations: Orthostatic Proteinuria.

(*a*) *Renal dynamic alterations and proteinuria following various stimuli:* Previous observations [27, 28, 29] and common clinical experience suggest that emotional stimuli play a role in orthostatic proteinuria, and that excitement may precipitate or aggravate orthostatic proteinuria. Emotional stimuli

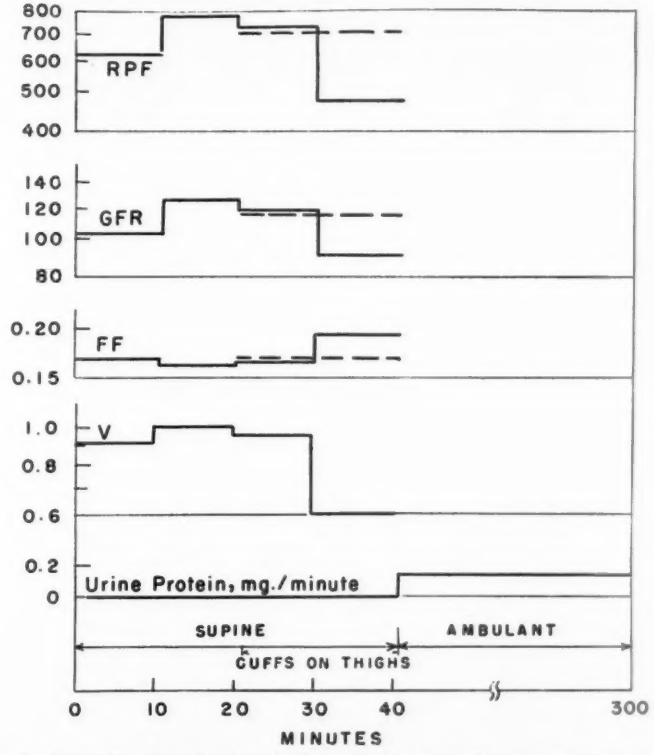

FIG. 3. The effect of application of thigh cuffs in a case of orthostatic proteinuria. In the supine position, application of thigh cuffs is followed by a fall in renal plasma flow (clearance of PAH), glomerular filtration rate (clearance of inulin) and urine volume rate. Proteinuria does not occur under these conditions, but appears after cuffs are removed and patient becomes ambulant.

apparently do not produce proteinuria in such subjects during recumbency. In over 50 observations, despite apprehension aroused by mechanical procedures involved in determinations of renal blood flow and functions by clearance methods, proteinuria did not appear in any instance during recumbency but occurred immediately on standing. In subsequent communications [38] it will be shown that subcutaneous epinephrine and application of thigh cuffs and abdominal binders in the supine position, although producing

alterations in renal hemodynamics and function similar to those in erect lordosis, were not followed by proteinuria (figures 2, 3).

Reduction in renal plasma flow (RPF) and glomerular filtration (GFR) in normal persons on standing, especially in lordosis, is well documented.[7] In a recent communication,[39] no difference was demonstrated in alterations in RPF and GFR in normal subjects and those with orthostatic proteinuria on change from the supine to the erect posture (figures 4, 5). Where proteinuria occurred on standing, no direct relationship was observed between the rate of protein excretion and renal dynamic variations. In normal subjects and in those with orthostatic proteinuria, only minor reduction

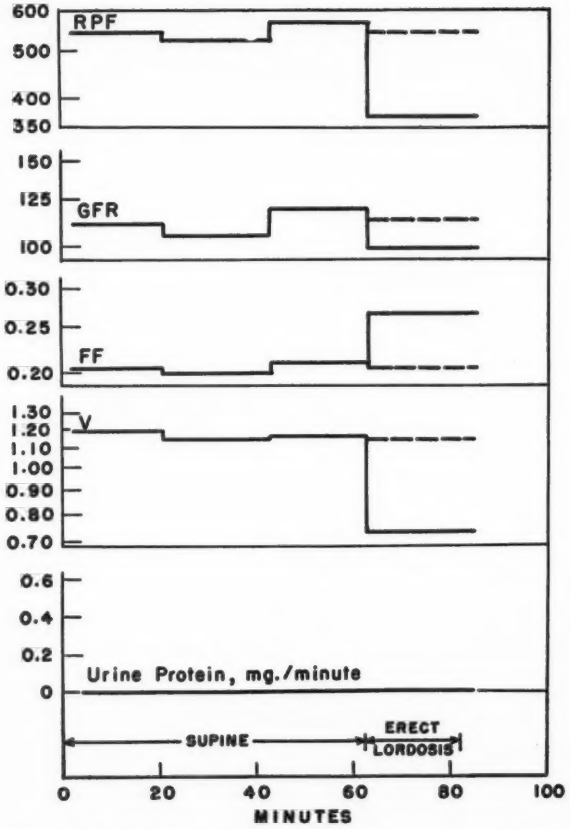

FIG. 4. The effect of posture on renal function in normal man. Upon change from supine position to erect lordosis there occurs a reduction in renal blood flow (clearance of PAH), glomerular filtration rate (clearance of inulin) and urine volume without proteinuria. The magnitude of these alterations is similar to those in figure 5.

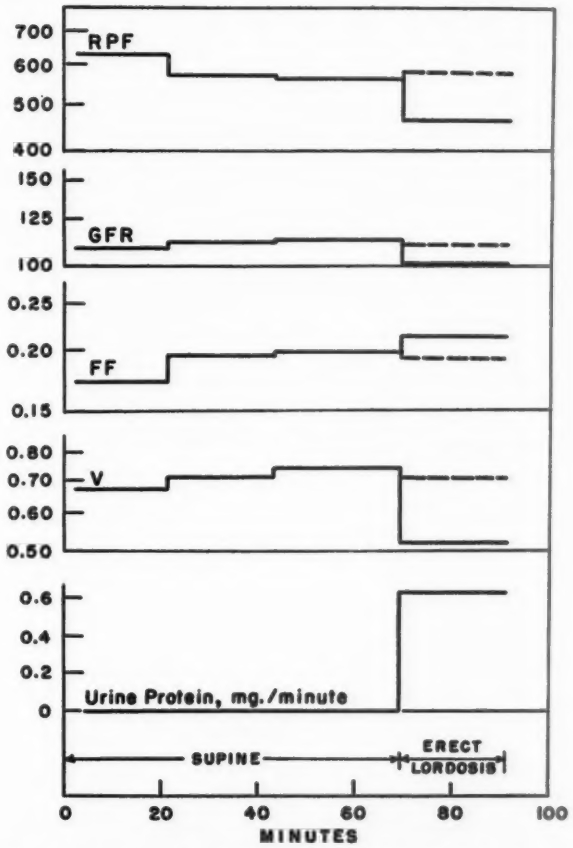

FIG. 5. The effect of posture in orthostatic proteinuria. Upon change from the supine position to erect lordosis there occurs a reduction in renal blood flow (clearance of PAH), glomerular filtration (clearance of inulin) and urine volume with moderate proteinuria. These alterations are similar to those in normal man.

occurred in tubular function, as measured by TM (PAH) and TM glucose, on changes from the supine to the erect lordosis.[38]

Orthostatic proteinuria is not limited to the erect lordotic position, and in some instances equally marked proteinuria and alterations in renal dynamics follow erect immobilization in kyphosis. In general, however, dynamic alterations, proteinuria and oliguria were most marked in erect, immobilized lordosis, frequently followed by syncopal reactions. Tilt and erect lordosis apparently produce maximal impediment of the peripheral venous circulation and most marked renal dynamic changes. Immobilization is an important factor.

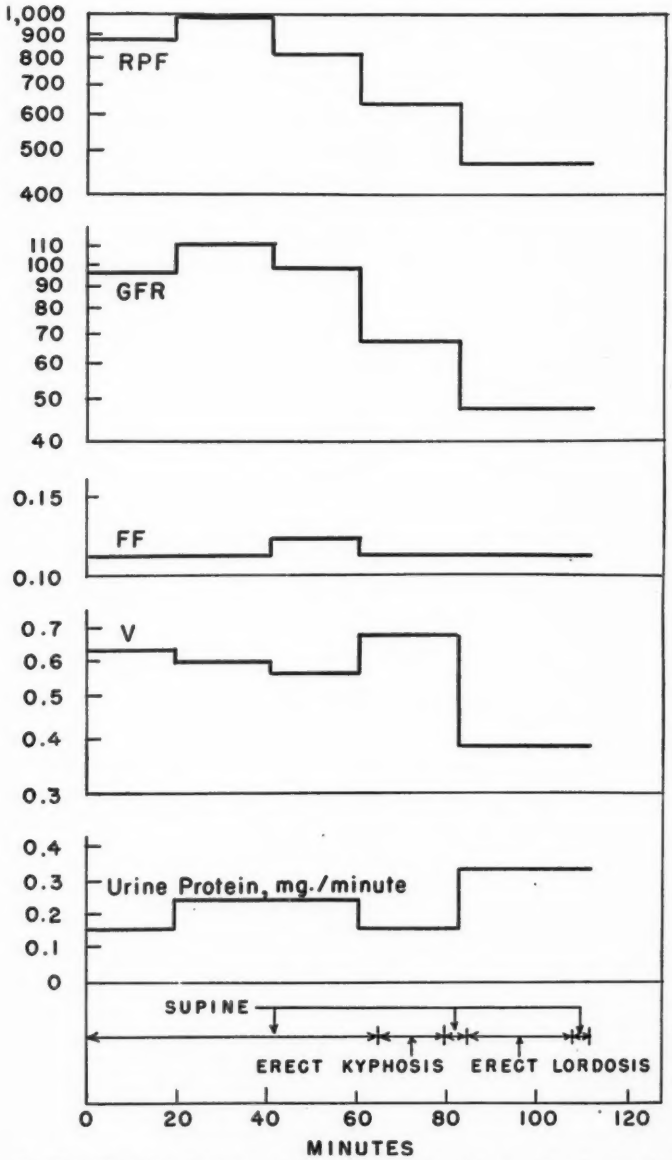

FIG. 6. The effect of posture upon renal functions and protein excretion in chronic nephritis (mild). Upon assuming the erect position there occurs a fall in renal plasma flow (clearance of PAH) and glomerular filtration rate (clearance of inulin) and urine volume. Protein excretion is moderately increased in erect lordosis.

(*b*) *Abdominal pressure and proteinuria:* Observations were made of the effect of increased abdominal pressure induced by tight binders (with pressure cuff), reaching 250 mm. water, in normal subjects and in patients with orthostatic proteinuria. In a subsequent communication [38] it will be shown that, with femoral vein pressures of 25 mm. of mercury and reductions in renal blood flow and glomerular filtration rates of 40%, proteinuria did not occur in normal subjects or in patients with orthostatic proteinuria while in the supine position. With the binder released, proteinuria occurred regularly in the latter subjects on standing.

(*c*) *The urine volume and proteinuria:* The rate of urine protein excretion was observed in approximately 30 subjects with orthostatic proteinuria under various conditions. Urine collections were obtained by catheterization, and accurate determination of the urine volume per minute (V) and protein excretion per minute (P) was possible. As previously mentioned, proteinuria occurred only on standing. No direct correlation between changes in volume (V), which were frequently marked (antidiuresis), and protein concentration was observed. Marked changes in volume were often not associated with proteinuria, which at times occurred with relatively unchanged moderate urine flow. There was no evidence in these preliminary observations to suggest that proteinuria is frequently due to excessive urinary concentration resulting, in effect, in a spurious proteinuria.

E. Physiologic Observations: Protein Excretion in Nephritis. It is usually stated that the rate of protein excretion in nephritis parallels the GFR, but it is also said that proteinuria is increased during the day.[7] As previously observed, the GFR normally diminishes in the erect position. Bradley [18] has described reduction in protein excretion in nephritis on standing. Protein excretion in response to postural change in two cases of nephritis is illustrated in figures 6 and 7. In figure 6 increased protein excretion followed standing, concurrent with a fall in GFR. Figure 7 illustrates proteinuria occurring in a case of chronic nephritis with severely impaired renal function. In this instance protein excretion paralleled the GFR, diminished on standing and increased in recumbency.

F. Physiologic Observations: The Quantity and Nature of the Proteins in Orthostatic Proteinuria. When estimated for the 24 hour period, the total urinary excretion of protein in orthostatic proteinuria rarely exceeds 1 gm. The effective rate of excretion and concentration of proteinuric urines in such patients may be considerable. Qualitative 4 plus reactions are frequent, and concentrations up to 4% have been reported.[40] In many instances in this study the effective rate of protein excretion was of the same order as that in chronic glomerulonephritis. In some cases the protein excretion rates approached 1 mg./min., with a mean of 0.5 mg./min. In other cases with severe orthostatic proteinuria, concentrations up to 0.3 gm.% in pooled day urines were not unusual. Specimens obtained at the height of proteinuria would have shown higher concentrations.

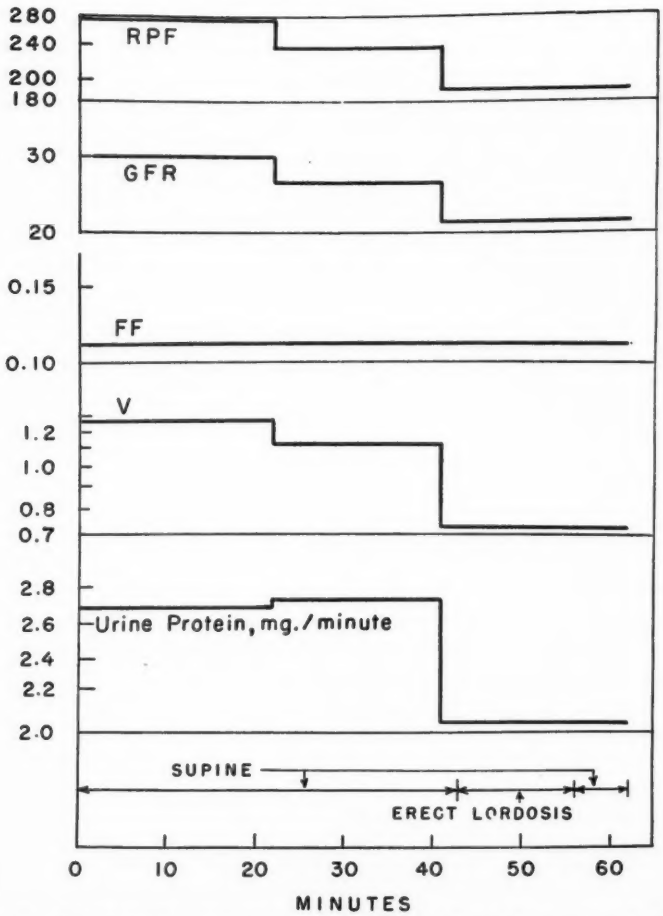

FIG. 7. The effect of posture upon renal functions and protein excretion in chronic nephritis (severe). Already severely diminished renal plasma flow (clearance of PAH) and glomerular filtration rate (clearance of inulin) are further reduced in erect lordosis. A moderate reduction in protein excretion occurs in erect lordosis in this instance.

Electrophoretic determinations of urine proteins were made in a group of selected cases of severe orthostatic proteinuria by the Tiselius and paper methods (point and line). The methodology proved laborious, requiring progressive concentration against concentrated solutions of dextran, in some instances, to one fortieth of initial volume, avoiding denaturization of the proteins. Any error in method favored loss of globulin as precipitate. Results (to be reported subsequently [41]) revealed considerable globulinuria. The A/G ratio of such urines determined by the Tiselius method was slightly

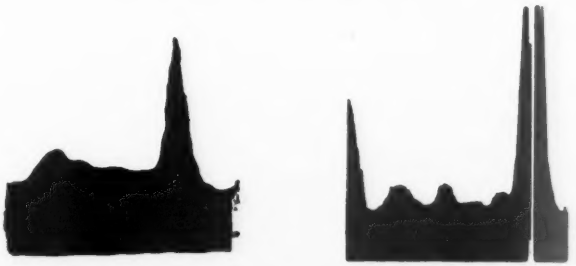

FIG. 8. The urinary proteins in patients with orthostatic proteinuria. Analysis of the urine proteins in two illustrative cases with orthostatic proteinuria by the Tiselius moving boundary method reveals considerable relative amounts of globulin in the alpha, beta and gamma fractions.

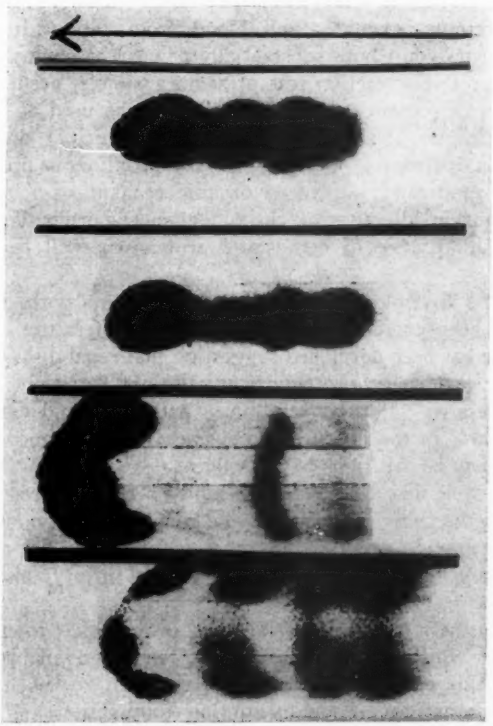

FIG. 9. The urinary proteins in patients with orthostatic proteinuria. Analysis of the urine from a number of representative cases with orthostatic proteinuria by paper electrophoresis reveals considerable quantities of globulin in various zones.

under 3. The relatively high proportions of globulin in the urines of some patients with orthostatic proteinuria is graphically demonstrated in figure 8 (Tiselius method) and in figure 9 (paper electrophoresis).

Discussion

Further experiences with the controlled urine protein excretion test are described in over 4,000 cases with proteinuria due to various conditions. The effects of variations in body fluid balance and urine volume upon protein detection are reviewed. Diuresis may dilute beyond detection even moderate quantities of protein due to disease. Variations in urinary volume are usually subject to control under set conditions, but emotional factors occasionally may induce diuresis even under hydropenic conditions. Although not evident in these patients, the possibility of spurious proteinuria during extreme oliguria from concentration of normally present proteins cannot be excluded. Nonrenal proteinuria may occur through contamination of urine by secretions, exudates and blood from the genitourinary tract. Laboratory errors contribute substantially to current confusion. The controlled urine protein excretion test presents a simple, accurate and reproducible pattern of protein excretion, which may be used as a point of reference to determine individual persistence (chronicity) and progression. It is accurate in differentiating orthostatic from continuous proteinuria. The latter implies moderately advanced organic renal disease, and it was invariably present in all cases of chronic glomerulonephritis in this study. The clinical significance of orthostatic proteinuria will be considered in detail.

Clinical and physiologic observations on patients with orthostatic proteinuria have been correlated with the available literature on the subject. Some evidence has been developed suggesting that renal diseases or disorders manifested by orthostatic proteinuria usually are persistent (chronic) and may be progressive. Impressive clinical, pathologic and experimental evidence is available in the literature to suggest that continued protein excretion in itself may be injurious to the kidneys.

A vicious cycle may be engendered which accelerates renal injury above the rate due to the primary disease. The globulinuria demonstrated in these patients, and temporary marked protein excretion rates, are compatible with the current physiologic concept of active renal injury, also indicated by urinary sediment abnormalities.[11, 30, 42]

The statement is frequently made that orthostatic proteinuria is a disorder of youth which tends to disappear. The few available reports in the literature on this aspect of the subject have been reviewed. In most instances albumin had been noted on routine examination, and the cases were subsequently followed in a variable, often casual fashion. Persistence of proteinuria was most conspicuous in the cases followed in considerable detail. A total of 194 followed cases with proteinuria has been collected from the

literature as follows: Palmer,[43] 35 cases; Thorp and Wakefield,[3] 64 cases; Young,[44] 14 cases; Bashford,[45] 30 cases; Fox,[46] 15 cases; Barringer,[47] 20 cases, and Addis,[11] 11 cases. Despite a varying selection of cases and follow-up methods, in 40 out of the 194 cases urinary protein persisted for extended periods of up to 30 years. Proteinuria persisted indefinitely in all instances studied by Addis, in 18 out of 64 in the study of Thorp and Wakefield, and in eight out of 20 in that of Barringer. In the last group, casts which were initially absent appeared in four of the eight persistent cases after an interval of 11 years. Incidentally, some of these reports [3] have been cited as the basis for the temporary and benign theory of orthostatic proteinuria. In many instances the fact that individuals were still alive or apparently well was accepted as evidence that the renal condition was insignificant. Three quarters of the 170 cases followed in this study and repeatedly examined by the conditioned urinary protein excretion test revealed persisting proteinuria for the entire period of individual observation (up to three years). A history of proteinuria of many years' duration was frequent. In conjunction with other evidence, it is believed that orthostatic proteinuria usually persists indefinitely.

Little has been contributed in this study to the etiology and pathology of orthostatic proteinuria except that it is obscure and probably of multiple origin. It may occur with hypertension and systemic diseases, and occasionally follows as a residue of otherwise apparently healed glomerulonephritis (healed with defect). Congenital renal defects were observed in about one fifth of a small group of cases studied by urography. Orthostatic proteinuria with organic disease, particularly large congenital defects, indicates progressive renal pathology, and the term "benign proteinuria" is particularly inappropriate under such circumstances.

The concept that orthostatic proteinuria is due to intermittent pressure upon the renal vein from congenital renal defects is based upon radiologic findings in isolated instances.[42] Intermittent renal vein obstruction from pressure on standing, or from kinks, ptotic kidneys and aberrant vessels, has been accepted by Addis [11] and others as the cause of orthostatic proteinuria. The frequency in normal persons of minor congenital variations such as bifid pelvis and ureters is well known.[7] The paucity of urologic data in patients with orthostatic proteinuria was emphasized by Bull [30] who, in developing a theory of his own, largely disposed of intrinsic renal defects as the sole major cause of orthostatic proteinuria. In the 18 cases studied by ureteral catheterization and reported in the literature, proteinuria was bilateral in about one-half. In the majority of cases no clear-cut etiology is apparent. Emotional factors and evidence of neurocirculatory inadequacy are conspicuous but not invariable. Pallor, sweating and syncope are frequent after simple procedures. Emotional stimuli may excite proteinuria in susceptible individuals as compared to normal controls, but apparently only in the erect position.[38]

Being an inconstant process of varying duration, the 24 hour output of

protein in patients with orthostatic proteinuria is rarely large. In more severe cases, effective excretion rates and urinary concentration of protein may be considerable. Instances of orthostatic proteinuria have been recorded in which protein excretion rates projected for 24 hours were in the same range as that of nephrosis.[2, 40] In a number of cases in this study, protein excretion rates approximating those of active glomerulonephritis were recorded. Furthermore, it must be recognized that the amount of protein appearing in the urine is no index of the concentration of protein in the glomerular filtrate. The latter is generally accepted as the injurious agent by advocates of this concept. Urinary protein in itself is prima-facie evidence of at least temporary, relative tubular impairment of function. The intense rate of urinary protein excretion and the considerable globulinuria in some cases suggest at least intermittent increase in glomerular protein filtrate of such magnitude as to overcome tubular reabsorptive capacity. It does not seem probable that the effects of tubular overloading disappear immediately, particularly if this process is repeated frequently and daily. Oliver [48] demonstrated that the period of intense tubular reabsorption (digestion) of protein extends for at least 17 hours. These considerations may be correlated with other accumulated evidence suggestive of injurious effects of continued proteinuria upon renal tubules and general nephron architecture.[10, 11, 18] Urinary protein determinations made in patients with orthostatic proteinuria by the Tiselius moving-boundary method and paper electrophoresis reveal considerable amounts of globulin in the urine occurring in about the same ratio to albumin as in the plasma. Globulinuria may be considered indicative of increased glomerular permeability,[17] or it may be due to marked glomerular protein filtration with preferential reabsorption of albumin. Oliver [48] states that he has never observed evidence of reabsorption of globulin by the renal tubules. Low A/G ratios have been reported by less accurate fractionation methods in orthostatic proteinuria as well as in acute and chronic nephritis with impaired function.[12] Its possible relation to further acceleration of renal damage has been reported.[18]

Attention is called to the frequency of cases with continuous proteinuria and normal sediment without history of prior renal disease. As maintained by Fishberg, the term "chronic nephritis" has become a rubric for a variety of conditions which include pyelonephritis and latent (healed with defect) glomerulonephritis. It is proposed that some renal disorders, manifested initially by orthostatic proteinuria, may contribute to instances of obscure "chronic nephritis." Progressive renal damage clearly occurs in some of the miscellaneous organic renal disorders manifested by orthostatic proteinuria. The clinical observation that patients initially diagnosed as "benign" orthostatic albuminuria subsequently develop renal disease called "chronic nephritis" is not rare.

Insurance Impairment Experiences: Interpretation of insurance company mortality experiences relating to proteinuria is confusing to the uninitiated.

The somewhat perplexing nomenclature is in part due to limitations on urine collections. Older experiences, particularly over the short term, did not suggest any significant difference between normal individuals and those with minor "intermittent" albuminuria. Daley [49] reported a greater mortality rate than anticipated (128% ± 5) among 52,000 individuals with "intermittent" albuminuria of small amount (10 to 50 mg.%). More recent experiences (to 1951 [50]) confirm this. Excess mortality rates for all individuals with intermittent albuminuria with trace of albumin were 150% ± 6. Excess mortality rates were greatest (191 ± 18%) in the period beginning 11 years after examination. Even in standard risks with intermittent albuminuria (trace), death from diseases of the heart and arteries was appreciably above normal, accounting for over two thirds of the excess mortality. Some cases with orthostatic proteinuria probably were included in these statistics as "persistent." The latter group, of course, had a much higher mortality rate. Recognizing limitations in application of these data it appears that individuals with orthostatic proteinuria may have an appreciably higher mortality than the normal population, particularly from disease of the vascular system, which becomes most evident a decade or more after initial discovery.

Obscure proteinuria frequently becomes an administrative as well as a clinical problem. Decisions are often necessary without opportunity for detailed observation or prolonged study. A practical formula is required for mass detection of individuals with potential renal disease. The frequency of proteinuria prohibits routine exclusion of such individuals from military service or other opportunity. Orthostatic proteinuria cannot be considered generally benign and inconsequential. This does not imply that casual proteinuria necessarily is cause for alarm. Most instances of proteinuria accidentally detected in apparently normal individuals are probably without significance. It is estimated that approximately 5% of all cases with proteinuria on single examination will represent continuous proteinuria, while about 15% will be instances of persistent, orthostatic proteinuria. Usually continuous proteinuria implies substantial organic renal disease. True orthostatic proteinuria cannot be dismissed without adequate study. If manifest organic renal pathology—particularly congenital defects, pyelonephritis and vascular disease—is excluded, the hazards of renal deterioration over short periods are remote. However, findings should be documented and reviewed to evaluate progression. It is doubtful that proteinuria of any kind, consistently present on repeated examination, justifies long-term obligations without detailed individual evaluation. The weakest link in the routine screening of renal disease is reliance upon a single casual urine specimen. An undetermined number of cases with proteinuria escape detection unless all collections are limited to morning specimens of adequate specific gravity.

It is improbable that the evolution and significance of orthostatic and other obscure proteinurias can be determined by individual clinical observa-

tion or through normal facilities of civilian medicine. Statistically adequate surveys appear to be the responsibility of governmental agencies. Such follow-up observations are indicated and practical within the facilities of the military and related services.

Summary

The conditioned urine protein excretion test has been applied to the study of a large heterogeneous group of renal disorders characterized by proteinuria of undetermined origin. Properly performed and intelligently interpreted, this test has proved accurate in differentiating cases with fixed, continuous proteinuria from those with orthostatic (inconstant) and variable proteinuria. Individual pattern consistency permits determination of persistence (chronicity) and progression or regression of obscure renal disorders in the absence of other laboratory or clinical indications.

Protein excretion by the kidneys follows simple, regular patterns of distribution: *negative, inconstant* or *orthostatic,* and *constant* or *continuous.* Continuous excretion of protein (day and night) indicates significant organic renal disease, bilateral or unilateral. It is invariable in active chronic glomerulonephritis and other conditions with serious renal injury, such as congenital renal defects and advanced chronic pyelonephritis. The term "orthostatic proteinuria" is purely descriptive, representing a pathophysiologic disturbance which may be due to a variety of renal disorders, organic and functional.

Despite the frequency of inconstant and variable and orthostatic proteinuria, the literature on the subject and medical practice are confused and contradictory. This is due in part to clinical neglect, because of the common belief that all cases are without significance, and in part to the previous lack of any accurate practical method for continued observation of such cases. The term "orthostatic proteinuria" is often used inaccurately to include the enormous numbers of instances of fleeting, accidental proteinuria discovered on routine examination of normal people. The possible causes of transient proteinuria have been considered.

In observations based upon approximately 15,000 young ambulatory individuals with initial proteinuria, approximately 5% represented cases with continuous proteinuria and 15% those with orthostatic proteinuria. It is difficult to accept an unqualifiedly benign prognosis for renal lesions which persisted indefinitely. Most cases (80%) with orthostatic proteinuria in this study persisted; many were due to demonstrable organic renal disease, including congenital renal defects, latent quiescent nephritis (healed with defect), early pyelonephritis and diffuse renal vascular disease. Clinically, these renal diseases are progressive, and the term "benign proteinuria" in such instances is manifestly incorrect. In the majority of cases with orthostatic proteinuria no renal lesion can be demonstrated. An unusually labile

response to emotion, posture and other stimuli is evident in many of these patients.

Little difference in magnitude of renal dynamic response to posture and various stimuli has been observed in normal individuals and those with fixed (organic) orthostatic proteinuria. Greater alterations in renal dynamics may occur with transient proteinuria. Effects of posture on proteinuria in nephritis are discussed. The possibility that proteinuria in some cases may be due to marked urinary concentration following antidiuretic effects of posture and emotion has been considered. For this reason proteinuria in small urine volumes should always be suspect.

Considerable quantities of protein may be excreted by patients with orthostatic proteinuria. In the more severe varieties (constant diurnal pattern), as much protein as in most cases of chronic nephritis may be excreted over the 24 hour period. Over short periods, high concentrations of urinary protein may be obtained. Electrophoretic determinations of urine proteins from a number of patients with severe orthostatic proteinuria revealed considerable amounts of globulin with an A/G ratio of 3. The considerable evidence suggesting injurious effects of continuous proteinuria upon the kidneys has been correlated with these findings. Globulinuria in particular is considered specifically more injurious and an evidence of greater damage than is albumin. Tubular reabsorption of protein is a function subject to strain and injury from continued overloading. The active destructive agent in continued proteinuria is considered to be the concentration and nature of the proteins in the glomerular filtrate. The pathologic physiology presents conditions compatible with progressive renal damage.

Various degrees of severity of orthostatic proteinuria are observed clinically. In the more severe, proteinuria is absent only at rest. Underlying organic conditions and the pathophysiology of proteinuria suggest—and clinical observation indicates—that some cases with orthostatic proteinuria may pass eventually into the continuous variety. Attention has been called to the frequency of cases of obscure continuous proteinuria with normal sediment, usually classified as latent glomerulonephritis. The opinion is ventured that they may represent advanced stages of miscellaneous conditions manifested initially by orthostatic proteinuria. Insurance impairment experiences indicate an appreciably greater (although delayed) mortality in individuals presenting intermittent proteinuria, even of slight degree, with disease of the heart and arteries as the major cause of the excess mortality.

Many questions and perhaps speculative possibilities have been presented which can be resolved only by suitable clinical observation. The frequency of these disorders and their possible impact upon chronic renal and perhaps vascular disease suggest that they merit greater attention and further study.

ADDENDUM

Since completion of this paper, transient proteinuria and renal ischemia have been observed repeatedly in man, in this laboratory, following intravenous norepinephrine and epinephrine.[51]

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HYPERCALCEMIA AND RENAL INSUFFICIENCY SECONDARY TO EXCESSIVE MILK AND ALKALI INTAKE*

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HYPERCALCEMIA associated with renal insufficiency has been reported in vitamin D intoxication,[1, 2] hyperparathyroidism,[3] acute osteoporosis,[4] sarcoidosis,[3, 5, 6] carcinomatosis with bone involvement[3, 7] and multiple myeloma.[3, 8] In 1949 the details of a new syndrome occurring in patients with symptoms of peptic ulcer ingesting large amounts of milk and absorbable alkali, and characterized by hypercalcemia (without hypercalciuria or hypophosphatemia), calcinosis and renal insufficiency, were described by Burnett, Commons, Albright and Howard.[9] Additional reports have appeared subsequently in the literature.[10-13, 27-30]

At a single hospital within a one-year period, out of a total of 291 patients with peptic ulcer, three patients were found who demonstrated the features of this syndrome, an incidence of 1%. Although this high rate of occurrence may represent a fortuitous observation, it suggests that this syndrome may be more common than was formerly suspected. In addition to pointing out the dangers attendant upon prolonged excessive milk and absorbable alkali intake, these cases demonstrate the relative improvement in renal function which may be brought about in many cases with appropriate therapy.

CASE REPORTS

Case 1. A 31 year old white male was admitted to the hospital on March 30, 1953, with a history of ulcer symptoms recurrent since 1945. In the last four years he had ingested daily two to four quarts of milk, two to three Alka-Seltzer tablets, and four teaspoonfuls of sodium bicarbonate. Greater amounts were ingested during exacerbations of epigastric pain. In 1950 a perforated duodenal ulcer was repaired surgically. The duration of the present symptoms of epigastric pain and intermittent vomiting was six weeks. No history of vitamin D intake was obtained.

Pertinent physical findings included an asthenic body build, a blood pressure of 180/120 mm. of Hg, arteriolar tortuosity in the ocular fundi, and a moderate degree of tenderness in the right epigastric region. Ocular calcification was absent.

Positive laboratory findings included a moderately severe hypochromic anemia, a urinary pH of 7.5, 1 plus albuminuria and numerous white blood cells per high power field. Serum calcium was 13.6 mg.%; phosphorus, 6.0 mg.%; nonprotein nitrogen, 87 mg.%; creatinine, 4.7 mg.%. Important normal laboratory examinations were the Sulkowitch test, urine culture, alkaline phosphatase, serum proteins and serum electrolytes, including the CO_2 combining power, sodium, potassium and chlorides. Roentgenologic examination revealed a contracted duodenal bulb. Chest

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x-ray, complete bone survey and x-rays of the lamina dura were normal. Electrocardiogram was normal.

Treatment consisted of Banthine, phenobarbital, nonabsorbable antacids, a low calcium diet (150 mg./day), and a high fluid intake. All symptoms subsided within a week. Elevated blood pressure levels returned to normal. Albuminuria, 1 to 2 plus, persisted throughout a two month period of hospitalization. On the low calcium diet there was a gradual decline in the serum calcium levels concomitant with a decline in the level of blood nonprotein nitrogen to 50 to 58 mg.%. Serum creatinine slowly decreased from 4.7 mg.% to 2.9 mg.%. Urinary calcium excretion, elevated at times early in the course of treatment, dropped to normal levels. Progressive improvement in phenolsulfonphthalein (PSP) excretion and the ability to concentrate urine was observed.

Evaluation six weeks after discharge revealed improvement in the hypochromic anemia. The serum calcium level had risen to 13.0 mg.%. Deterioration in the ability to excrete PSP and to concentrate urine was evident. Despite two negative urine cultures a course of antibiotic therapy for suspected pyelonephritis was given. The low calcium diet and high fluid intake were ordered continued following discharge.

In October, 1953, the patient was re-admitted with complaints of persistent mild weakness and tarry stools one month previously. He claimed to have maintained the prescribed regimen.

Blood pressure was normal and physical examination noncontributory.

Hypochromic anemia was again present. Urinalysis showed a pH of 6.0 to 7.0 and an occasional trace of albumin. Serum calcium was 9.3 mg.%; nonprotein nitrogen, 45 mg.%; urinary calcium excretion, 23 mg./24 hours. Occult blood was present in the stool. No significant change in PSP excretion or urinary concentrating ability was observed.

Improvement in symptoms occurred following blood transfusion and ferrous gluconate administration. Occult blood disappeared from the stools and the patient was discharged. The effect of the low calcium diet on the chemical constituents of the blood and renal function is illustrated in figure 1.

Case 2. A 54 year old white male painter was admitted to the hospital for the first time on September 26, 1952, with complaints of gnawing epigastric pain for 15 years. For many years pain had been relieved by 8 to 10 teaspoonfuls of Sippy powder daily. However, more recently, with a decline in the effectiveness of the regimen, he had ingested similar amounts of sodium bicarbonate. For the last five years his milk intake has been a minimum of one quart per day. Vomiting occurred almost daily during the 15-year period of illness, and in the last two or three years considerable gastric retention developed. On two occasions, three and one months prior to admission, tarry stools were noted. There was no history of vitamin D intake.

The past history revealed the occasional occurrence of substernal pain, mild dyspnea and peripheral edema, for which he had been hospitalized elsewhere a year before the present admission. Treatment consisting of a salt-free diet and digitalis had resulted in the disappearance of symptoms. Subsequently the patient discontinued the salt-free diet and digitalis therapy without recurrence of symptoms. There was a history of hypertension of two or three months' duration.

The pertinent physical findings included a blood pressure of 180/120 mm. of Hg, arteriolar narrowing in the ocular fundi, a slight amount of tenderness in the epigastric region, a liver palpable 3 cm. below the right costal margin and a small amount of pedal edema. Ocular calcification was absent.

The laboratory data included a normal hemogram, and an alkaline urine containing a trace of albumin and 10 to 12 leukocytes in the sediment. Serum calcium con-

centration was 13.5 mg.%; phosphorus, 5.4 mg.%; nonprotein nitrogen, 66 mg.%; creatinine, 4.2 mg.%; CO_3 combining power, 31 mEq./L. Alkaline phosphatase, serum proteins, liver function tests, serum sodium, potassium and chlorides were normal. Urine culture was negative. Phenolsulfonphthalein excretion and the ability to concentrate urine were impaired. Roentgenologic studies revealed an ulcer on the lesser curvature of the stomach and 30% retention of barium in four hours, a right renal calculus and calcification in the area of the internal carotid artery above the sella turcica. X-rays of the chest, long bones, pelvis and the lamina dura were

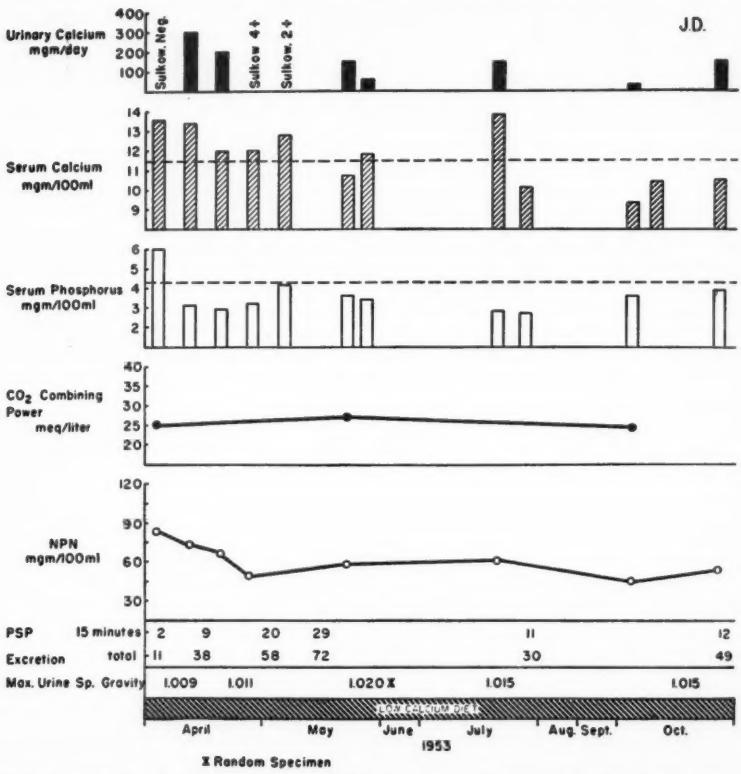

FIG. 1. Effects of therapy. No absorbable alkali intake during period of observation.

normal. Electrocardiogram showed changes consistent with left ventricular hypertrophy and/or myocardial damage.

Parenteral fluids and gastric suction for two days and subsequent treatment with antispasmodics, sedatives and nonabsorbable antacids produced a remission. A low calcium diet was continued for only two weeks. During this time serum calcium, phosphorus and nonprotein nitrogen levels declined to normal, but the CO_3 combining power did not change. Urinary calcium excretion was within the normal range. Hypertension disappeared within two days. When the patient's condition became stabilized a subtotal gastrectomy was performed and recovery was uneventful.

Three months later the patient was re-admitted to the hospital with findings typical of homologous serum hepatitis, from which he recovered without complications. During this hospitalization the serum calcim level was found to be normal, and marked improvement in phenolsulfonphthalein excretion and the ability to concentrate urine was observed. The course and the important laboratory data are illustrated in figure 2.

Case 3. A 57 year old white male had ulcer symptoms dating back to 1925. Relief had been obtained for many years by the ingestion of four or five teaspoonfuls

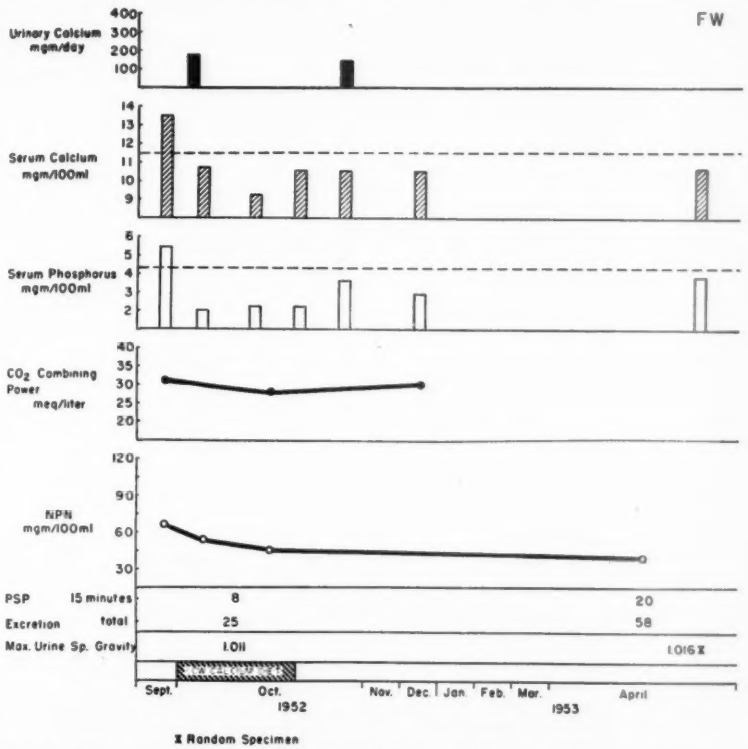

FIG. 2. Effects of therapy. No absorbable alkali intake during period of observation.

of sodium bicarbonate daily. For four years preceding his first hospital admission he had ingested a minimum of one quart of milk per day. His past history revealed the occurrence of asthmatic attacks since 1928, hospitalizations in 1935 for dyspnea and chest pain, and again in 1945 for hypertension and a cerebrovascular accident.

At the time of his hospital admission in January, 1952, the blood pressure was 180/96 mm. of Hg, the ocular fundi showed a grade I hypertensive retinopathy, and there were mild wheezing throughout the lung fields, emphysema, epigastric tenderness and poor dorsalis pedis pulsations.

The urine was persistently alkaline and contained a trace to 2 plus albumin. The blood nonprotein nitrogen was normal, but the CO_2 combining power was 34 mEq/L.

Excretion of phenolsulfonphthalein was reduced, and the ability to concentrate urine was slightly impaired. X-ray examinations demonstrated a deformed duodenal bulb, calcification within the splenic vessels, the abdominal aorta and the pelvic vessels, and a normally functioning gall-bladder. An electrocardiogram indicated a previous anteroseptal infarction and right bundle branch block.

Following this hospitalization the patient discontinued the use of sodium bicarbonate but continued the ingestion of large amounts of milk.

During another hospital admission, in August, 1952, for a recurrence of severe epigastric pain, the serum calcium level was found to be 12.3 mg.%. The urine was alkaline and contained a trace of albumin and sugar and 5 to 15 white blood cells per high power field, with occasional clumps of leukocytes.

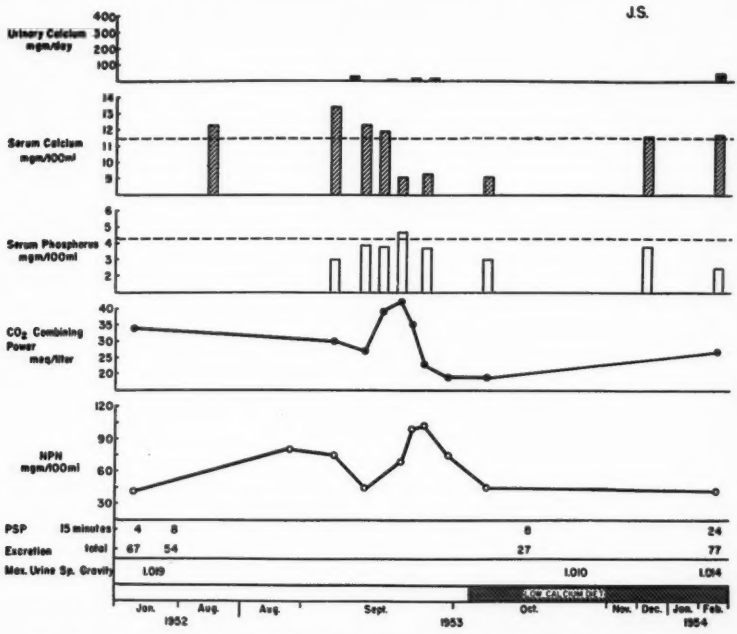

FIG. 3. Effects of therapy. No absorbable alkali intake since February, 1952.

A remission occurred following therapy including a bland diet, sedatives, antispasmodics and nonabsorbable alkali.

The patient was not seen again until the latter part of August, 1953, when he was admitted to the hospital with complaints of epigastric pain, vomiting and tarry stools. The patient gave no history of vitamin D intake.

On physical examination dehydration was evident, the blood pressure was 120/90 mm. of Hg, there was marked tenderness in the epigastric region, and "dark" stool was found in the rectum. Ocular calcification was absent.

The laboratory findings included a normal hemogram, a urinary pH of 7.5, 20 to 35 leukocytes per high power field with occasional clumping, and 4 to 10 erythrocytes per high power field. The stool contained occult blood. Serum calcium was 13.4 mg.%; phosphorus, 3.0 mg.%; nonprotein nitrogen, 82 mg.%; creatinine, 2.5 mg.%;

CO_2 combining power, 30 mEq/L.; serum sodium, 153 mEq/L. The alkaline phosphatase, total serum proteins and A/G ratio, serum potassium and chlorides were normal. Urinary calcium excretion was 21 mg. in 24 hours. X-ray examinations demonstrated calcification within the femoral vessels and spleen. The bones and lamina dura were normal.

Following adequate hydration the blood nonprotein nitrogen level, CO_2 combining power and serum sodium concentration declined to normal levels. The hemoglobin concentration dropped from 14.5 gm.% to 11 gm.%, and the hematocrit from 47% to 35%. Because of persistent pyloric obstruction a posterior gastroenterostomy was performed on September 14, 1953. Within 24 hours a severe metabolic alkalosis developed, associated with a rapid rise in the blood nonprotein nitrogen concentration, and a decrease in the serum calcium, sodium and chloride concentrations. Clinical tetany was evident. When ammonium chloride and calcium gluconate proved ineffective, the administration of sodium- and potassium-containing solutions produced striking improvement, and eventuated in recovery of the patient, both clinically and chemically. On October 7, 1953, the patient was placed on a low calcium diet and a high fluid intake. Phenolsulfonphthalein excretion and the ability to concentrate urine were poor. *Aerobacter aerogenes* was isolated from the urine and treated successfully with Aureomycin. In December, 1953, the serum calcium level was 11.6 mg.%. The blood pressure had risen to 160/96 mm. of Hg.

Reëvaluation of the patient in February, 1954, after four months of treatment with a low calcium diet, revealed the serum calcium level to be 11.7 mg.%. Urinary pH was now 5.0, and only an occasional erythrocyte and leukocyte were seen in the sediment. Phenolsulfonphthalein excretion improved markedly, and the ability to concentrate urine slightly. The blood nonprotein nitrogen content, CO_2 combining power and urinary calcium excretion were normal. The patient has been symptom-free while on the present regimen. The course and the pertinent laboratory data are illustrated in figure 3.

Discussion

Twenty-one cases of the syndrome of hypercalcemia and renal insufficiency secondary to prolonged excessive milk and absorbable alkali intake, including the three cases comprising the present report, have been reported to date. The important clinical characteristics are given in table 1. In all instances but one [28] the patients have ingested both milk and absorbable alkali; in the latter case the patient ingested only absorbable alkali.

Ocular lesions have been encountered in 16 of 21 instances. In none of the author's cases have ocular lesions been noted. The lesions, best seen with the aid of a slit lamp, consist of band keratitis, of crescentic deposits of calcium in the margins of the cornea, most prominent on the nasal and temporal sides, and of small crystalline deposits of calcium in the conjunctiva of the palpebral fissure area. These may be found singly or in combination. The findings are most probably due to hypercalcemia per se, and have been described in detail in other hypercalcemic conditions.[14]

Calcinosis, excluding the ocular lesions, was detected in 18 of the 21 cases. The distribution of the sites of calcium deposition is summarized in table 2. Within the kidneys the calcium deposits are located in the tubular lumina and within the tubular cells.[12] Nephrolithiasis has been noted three times,[9, 13] in addition to case 2 of the present report. Of the

TABLE 1
Pertinent Clinical Data

Author	No. of Cases	High Milk Intake	Absorbable Alkali Intake	Ocular Lesions	Calcinosis	Hypercalcemia	Serum Eleva.	Phos. Norm.	Azotemia	Alkalosis	Normal Urine Calcium	Urine pH above 6.0	Albuminuria	Impaired Tubular Function	Pyuria	Pyelonephritis
1. Burnett et al.[9]	6	6	6	6	5	5	4	2	6	5	5	2 3 not recorded	5	6	3	1
2. Kirsner[10]	1	1	1	0	1	1	1	0	1	1	1	1	1	1	0	0
3. Miller et al.[11]	1	1	1	1	1	1	0	1	1	1	not recorded	1	1	1	0	0
4. McQueen[29]	1	1	1	1	1	1	0	1	1	1	not recorded	1	1	1	0	0
5. Wermer et al.[12]	1	1	1	1	1	1	0	1	1	0	1	not recorded	1	1	1	0
6. Dufault and Tobias[13]	4	4	4	3	3	4	2	2	4	3	1 3 not recorded	not recorded	4	4	2	1
7. Dworetzky[27]	1	1	1	1	1	0	0	1	1	0	1	not recorded	1	1	1	1
8. Snapper et al.[28]	2	1	2	2	2	1	2	0	2	1 not present 1 not recorded	1 not recorded	1	2	2	1	0
9. Foltz[30]	1	1	1	1	1	1	0	1	1	0	1	1	1	1	0	0
10: Kessler	3	3	3	0	2	3	2	1	3	2	3	3	3	3	2	1

six instances of nephrocalcinosis, five were detected by conventional clinical studies and one [12] was found only on microscopic examination of the kidney after necropsy. The microscopic deposition of calcium in the renal tubules has been reported in other conditions involving alkali ingestion or acute alkalosis.[15, 16] This would suggest that renal calcinosis can occur without being detected clinically, and may indeed have been present in case 1, who showed no clinical evidence of metastatic calcification.

Subcutaneous calcification has been found in such diverse sites as the lumbar region,[11] the elbows, hands and knees,[9, 13] the shoulder, apparently in the region of the subacromial bursa, the wrist, and at the angle of the scapula attached to periosteum,[12] and in the subdeltoid bursa and region of the tuberosity of the ischium.[13] Within the lungs deposits of calcium have been noted in the alveolar septa,[12] and they have been sufficiently prominent to outline the bronchi on an x-ray of the chest.[9] The walls of the arteries have been extensively involved, and involvement has been observed in the

TABLE 2

Distribution of Calcinosis

Sites of Calcium Deposition		Frequency
1. Kidneys	Parenchyma	6
	Calculi	4
2. Subcutaneous Tissue		9
3. Blood Vessels		9
4. Lungs	Parenchyma	3
	Bronchi	1
5. Brain	Parenchyma	1
	Dura	3
6. Periosteum		2
7. Bone		2
8. Muscle		1
9. Tendons		1
10. Lymph Nodes		1

aorta and in the renal, femoral, iliac, splenic and carotid vessels.[9, 12] The linings of the brain have been the site of calcium deposits in three instances,[9, 13] and the brain substance once.[10] Of the original cases reported by Burnett et al.,[9] one showed an increase in the density of the cancellous bone, and another extensive periosteal new bone formation. In another report [12] a soft tissue calcification was attached to the periosteum of the scapula. The costal cartilages, diaphragm, tendons and abdominal lymph nodes were involved once each.[9]

Hypercalcemia was present in 18 of 21 cases. In one the serum calcium level was considered to be borderline.[9] In the remaining two cases [27, 28] therapy had been instituted before the serum calcium concentration was determined. Elevated serum phosphorus concentrations were present in nine cases and normal levels were observed in the remaining ones. In no instance was hypophosphatemia reported. The low concentration of phosphorus in the serum reported in one case [30] was considered to be a laboratory error.

Azotemia of varying degree was present in all 21 patients. Alkalosis was observed in 13 patients. The alkalosis has generally been found to be mild, but has been recorded as high as 40 mEq./L.[18] Urinary calcium excretion was measured in 15 patients and found to be normal in 14.

The urinary pH was recorded in 12 cases and found to be above 6.0 in 10. Albuminuria varying from a trace to 4 plus was noted in 20 cases. Renal function as measured by phenolsulfonphthalein excretion or urea clearance was impaired in all 21 cases. Hyposthenuria was observed in 20 instances. In two patients renal hemodynamics and maximal tubular excretory capacities were studied.[9] Glomerular filtration rate, effective renal plasma flow and maximal tubular excretory capacity were markedly reduced. Ten patients exhibited pyuria, but pyelonephritis could be established definitely only in case 3 and in three other cases.[9, 18, 27] However, in one case[9] pyelonephritis was diagnosed at necropsy; a positive urine culture was not obtained during life.

Certain aspects of the effects of hypercalcemia require comment because the basic feature in the syndrome is the renal damage which results therefrom. When the serum calcium level is raised by the intravenous administration of calcium salts, an abrupt increase in the urinary excretion of calcium occurs.[17] Hypercalciuria is usually seen in hypercalcemic syndromes other than the one under discussion.[1, 3, 4, 6, 8] The absence of hypercalciuria in the patients with the present syndrome suggests some type of interference with the normal renal mechanism for the excretion of calcium. That alkalosis plays a rôle in the renal handling of calcium is an interesting speculation, since it has been demonstrated that alkali administration decreases urinary calcium excretion,[3] while ammonium chloride ingestion results in increased calcium excretion.[18] Of potential importance, also, is the observation that orally administered inorganic phosphate decreases the urinary excretion of calcium.[17] The ramifications of this observation may be considered in terms of the knowledge that milk contains large amounts of phosphate in addition to calcium. Whatever the explanation for the lack of hypercalciuria may be, it is certain that a decreased urinary pH in association with an increased filtered load of calcium will enhance the precipitation of calcium in the renal tubules.

There is no reason to believe that the mechanism of the renal calcium deposition in this syndrome is different from that of other hypercalcemic syndromes. The initial calcium deposits leading to nephrolithiasis occur in the parenchyma just beneath the tubular epithelium.[19] They slowly protrude into the lumen, destroying the overlying tubular epithelium, and subsequently lodge there, forming the nidus for a calcium stone.[20] In other instances casts of calcium may form which obstruct the tubules and produce tubular dilatation. Substantiating this view is the observation that calcium casts may develop in any alkaline urine, provided the urine contains a large amount of calcium and phosphate, as would be the case in an individual who ingests large amounts of milk.[3] In addition, it is considered by Al-

bright and his co-workers [21] that these casts may initiate inflammatory changes in the kidneys which result in sclerosis and contracted kidneys. Anderson,[22] however, considers that interstitial deposits of calcium may have even greater importance than the intraluminal ones, but that primary renal damage determines the location of the calcium deposits. The description of the renal lesions in hyperparathyroidism[20, 21, 22] conforms so closely to the description by Wermer, Kuschner and Riley [12] of the only case of the condition under discussion in which the microscopic anatomy has been described completely that quoting their report seems worth while: "The renal capsule was thickened. Numerous glomeruli showed partial to complete hyalinization and thickening of Bowman's capsule was a prominent feature. In the areas of glomerular hyalinization there was marked tubular atrophy with increase in the interstitial connective tissue in which diffuse lymphocytic infiltration was seen. The more normal tubules were dilated and hypertrophied. The striking feature was the extensive calcification of renal convoluted tubular cells and in some cases the deposition of calcium masses in the tubular lumina. Large aggregates of calcium were seen beneath and bulging into the calyceal mucosa. The arterioles were not prominent. There was some intimal thickening of the small and medium-sized arteries."

It is of interest that, of the 10 cases which exhibited varying degrees of microscopic pyuria, only four were proved to have pyelonephritis. The suspicion of pyelonephritis in case 1 was sufficiently strong to result in therapy for pyelonephritis despite persistently negative urine cultures. It is conceivable, considering the microscopic anatomy and the similarity to hyperparathyroidism, that the pyuria is secondary to renal inflammatory changes associated with calcium deposition but without actual infection. The development of active pyelonephritis would be considered to be a less common complication of the calcium deposits and the inflammatory changes. To be sure, however, where there is preëxisting pyelonephritis, calcium deposition would be expected to occur more readily.

The origin of the hypercalcemia observed in this syndrome is not apparent from the data available. The oral administration of milk in the normal individual has not been reported to elevate the serum calcium level unless the milk has been acidified. The rise so produced amounts to roughly 1 mg.%.[23] This indicates the difficulty in raising the serum calcium by milk ingestion. Whether the hyperchlorhydria commonly found in patients with peptic ulcer will aid in the absorption of calcium over a prolonged period and produce hypercalcemia is purely conjectural. Probably the major contributory factor to the hypercalcemia is the inability of the kidney to excrete the increased load of calcium. The question of whether the increased amount of phosphorus ingested via the milk contributes to the hypercalcemia arises. However, it has not been demonstrated with any certainty that phosphate will affect the absorption of calcium from the gastrointestinal tract in man.[24] On the other hand, the elevated serum

phosphorus level observed in over half the cases is probably the result of depression of parathyroid activity brought about by hypercalcemia.[25]

The solubility product of calcium times phosphorus is equal to about 40. Normally, an excess of either ion brings about removal of the other by excretory means, thereby maintaining homeostasis.[26] When values above 40 develop, danger of metastatic calcification increases.[25] Since the serum calcium level in this syndrome is always elevated and the phosphorus frequently elevated, a situation favoring metastatic calcium deposition would obtain. This, indeed, appears to be the case.

Therapy in all recorded instances has consisted of a low calcium diet and withdrawal of absorbable alkali. In some cases a high fluid intake was given in addition; however, this did not appear to have any bearing on the outcome. Other measures generally included in the therapeutic regimen for peptic ulcer, as the use of antispasmodics and proper diet, were carried out. The administration of nonabsorbable alkali in the form of aluminum hydroxide gel and magnesium trisilicate has been used without any demonstrable detrimental effect. The effects of therapy are given in table 3.

The ocular lesions improved but did not disappear in three of the five cases in whom follow-up observations were recorded. In one of these [13] improvement occurred following the use of a calcium-binding agent, locally administered. Calcinosis elsewhere improved in only three cases, and here the changes were dramatic.[12, 27, 29] In contrast, the effects on the serum calcium and phosphorus were marked and constant. In all cases the concentration of calcium in the serum declined to normal levels, as did the concentration of phosphorus in the nine cases in whom it was initially elevated. A subsequent rise in serum calcium concentration was attributed to an increased calcium intake.[29] In most instances the phosphorus levels declined even more rapidly than the calcium. Of the 13 cases in whom alkalosis was present, improvement occurred in nine; there was no change in the remaining ones.

Renal function as measured by the degree of azotemia, phenosulfonphthalein excretion and the ability to concentrate urine improved in only 10 of the reported cases. The improvement varied from the total disappearance of the renal defects to only slight improvement. In one case,[12] after a slight initial improvement function deteriorated progressively. In four others deterioration progressed despite therapy. No improvement was noted in the remaining cases. In case 1 there was, however, a significant improvement initially, followed by a subsequent deterioration in function. The explanation for this is not apparent. The effects of therapy on the degree of albuminuria and pyuria were not recorded in a sufficient number of cases to permit analysis. However, it may be mentioned that in the three cases reported by the author, albuminuria decreased in one case and disappeared in two. Pyuria diminished in the two instances in which it had been present. No statement can be made about the effect of treatment on the urinary pH.

TABLE 3

Effects of Therapy; Use of Low Calcium Diet and No Absorbable Alkali Intake

Author	No. of Cases	Ocular Lesions	Calcinosis	Serum Calcium	Serum Phosphorus	Alkalosis	Renal Function	Died	Cause of Death
1. Burnett et al.	6	Not recorded	Not recorded	6 Improved	2 Normal 4 Improved	1 Not present 2 Unchanged 2 Improved 1 Not recorded	3 Improved 2 Deteriorated 1 Unchanged	4	2 Renal failure 2 Unknown
2. Kirsner	1	Not present	Not recorded	Improved	Improved	Improved	Improved	0	—
3. Miller et al.	1	Unchanged	Unchanged	Improved	Normal	Improved	Improved	0	—
4. McQueen	1	Not recorded	Improved	Improved*	Normal	Improved	Unchanged	0	—
5. Wermer et al.	1	Improved	Improved	Improved	Improved	Not present	Deteriorated	1	Bleeding ulcer and renal failure
6. Dufault and Tobias	4	1 Improved 1 Not present 2 Not recorded	1 Unchanged 1 Not present 2 Not recorded	4 Improved	2 Improved 2 Normal	3 Improved 1 Not present	2 Improved 1 Deteriorated 1 Unchanged	1	Renal failure
7. Dworetzky	1	Improved	Improved	Normal	Normal	Not present	Unchanged	0	—
8. Snapper et al.	2	Not recorded	Not recorded	1 Normal 1 Not recorded	1 Unchanged 1 Not recorded	1 Not present 1 Not recorded	1 Deteriorated 1 Not recorded	1	Renal failure
9. Foltz	1	Not recorded	Not recorded	Improved	Normal	Not present	Improved	0	—
10. Kessler	3	Not present	2 Unchanged 1 Not present	3 Improved	2 Improved 1 Normal	1 Improved 1 Unchanged 1 Not present	2 Improved 1 Unchanged	0	—

* Relapse when patient deviated from his diet.

Seven deaths have occurred in the 21 recorded cases. In five, renal failure was the cause of death or contributed greatly, and in two cases the cause was unknown. It is interesting to note that when the renal disease progressed to death, the clinical picture changed and appeared identical to that seen in other cases of progressive renal insufficiency. The clinical findings in these circumstances included hypocalcemia, hyperphosphatemia and acidosis in varying degree.

Since the severity of the renal disease and the response of the kidney to therapy vary widely, the prognosis in this condition appears to be related directly to the duration and severity of the renal disease. It is important, therefore, to maintain an awareness of the potentially dangerous effects of prolonged excessive milk and absorbable alkali intake, and to initiate an investigation for this syndrome in any patient presenting a history of such intake. Suspicion should be further enhanced by the presence of an alkaline urine. This awareness will permit the early institution of proper therapy.

Other causes for hypercalcemia and renal insufficiency—for example, vitamin D intoxication, hyperparathyroidism, acute osteoporosis, sarcoidosis, carcinomatosis with bone involvement and multiple myeloma—may generally be ruled out by various differences in the history, physical findings, laboratory findings and/or the clinical course. Thus, vitamin D intoxication may be differentiated by the history of vitamin D intake and frequently an elevated alkaline phosphatase; hyperparathyroidism with renal disease by bony involvement, when present, and by the lack of improvement on a low calcium intake; acute osteoporosis by the history of prolonged inactivity and the presence of bone demineralization; and sarcoidosis, carcinomatosis with bone involvement and multiple myeloma by obvious differences in the clinical picture. In these hypercalcemic syndromes hypercalciuria is common, while the hypercalcemic syndrome due to milk and absorbable alkali intake is the only one wherein low or normal urinary calcium excretion is found consistently.

Summary

Three cases are presented of a syndrome characterized by hypercalcemia without hypercalciuria or hypophosphatemia, calcinosis and renal insufficiency, and occurring in patients with a prolonged history of excessive milk and absorbable alkali intake.

A review is given of the features in all of the cases reported to date.

Improved renal function and partial correction of the chemical abnormalities have been obtained in many instances by placing the patients on a diet low in calcium and absorbable alkali.

The prognosis appears to depend on the duration and severity of the renal disease.

The pathogenesis and differential diagnosis are discussed.

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BENIGN GASTRIC POLYPS *

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BENIGN polyps of the stomach were discovered in 32 patients at the Los Angeles County Hospital between 1943 and 1953, approximately a 10 year period. These polyps were both sessile and pedunculated, single and multiple, and those studied histologically were all adenomatous.

Table 1 shows age-sex distribution. There was no appreciable sex difference. The majority were found in patients in their seventh and eighth decades. Incidentally, the racial distribution corresponded to that of the hospital population as a whole, approximately 2:1, Caucasian to Negro.

The diagnostic procedures are noted in table 2. Twenty-three patients had upper gastrointestinal series, and in only three of these was a definite diagnosis of polyps established. Thirteen were diagnosed as "abnormal stomach" without further clarification. In seven, "normal stomach" was reported.

TABLE 1

Age-Sex Distribution of Benign Gastric Polyps

	20–29	30–39	40–49	50–59	60–69	70–79	80–89	90–99	
Males			2	2	5	6	1	1	17
Females	1	2	1	2	7		2		15
								Total	32

Gastroscopy was performed in 21 patients, with a definitive diagnosis of benign polyp or polyps in 15. In three additional patients a polyp was observed gastroscopically, but the endoscopist was unable to exclude malignancy with certainty. In the three remaining patients, existing polyps were not visualized. Of the last group, surgery confirmed the presence of polyp in two cases, while x-ray was the only positive evidence in the remaining case.

Surgery was performed and was confirmatory in eight patients. Of the eight, four had been previously diagnosed gastroscopically, while two had not been subjected to the procedure. In the remaining two patients,

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polyps were not visualized. X-rays of the patients in this group were diagnostic in one and questionable in seven. Both x-rays and gastroscopy were positive in only a single case.

TABLE 2

Diagnosis of Benign Gastric Polyps

X-Ray		23
Definite diagnosis	3	
Diagnosed as abnormal stomach	13	
Normal stomach	7	
Gastroscopy		21
Positive diagnosis	15	
Benign polyps vs. malignancy	3	
Missed polyps	3	
Surgery		8
Diagnosed by gastroscopy	4	
Missed by gastroscopy	2	
Not gastroscoped	2	
X-rays—1 definite and 7 questionable		
X-ray and gastroscopy—positive in 1 case only		
Postmortem		9
X-ray—negative	1	
Total Cases		32

Autopsy disclosed the presence of polyps incidentally in nine patients. In this group, the only diagnostic procedure was a single x-ray and this was negative.

TABLE 3

Symptoms

Abdominal pain (vague to definite pain)	16
Weight loss	14
Vomiting	10
Nausea	8
Anorexia	6
Melena	4
Hematemesis	3
Regurgitation	3
Anemia	2
Pyrosis	1
Diarrhea	1
Weakness	1
No symptoms	7

Table 3 shows the frequency of symptoms. It is interesting to note that seven cases had no symptoms referable to the gastrointestinal tract. No single diagnostic criterion was observed consistently. The following case report is illustrative:

CASE REPORT

A 63 year old white female gave a four year history of epigastric pain, worse at night and relieved by cream and alkalies. Hematemesis made her seek hospitalization.

Upper gastrointestinal series showed 30 per cent retention in six hours. The distal third of the stomach was diffusely and markedly narrowed. A diagnosis of carcinoma of the pyloric end of the stomach was made (figure 1).

Gastroscopy revealed a normal distal third of the stomach. The mucosa of the body, however, was the site of innumerable sessile, polypoid masses 1 to 2 cm. in diameter. Several areas of bleeding were noted. The diagnosis was benign polyposis, with malignant change not definitely excluded.

Total gastrectomy was performed and the benign nature of the polyps was confirmed. The patient has remained well for the past five years.

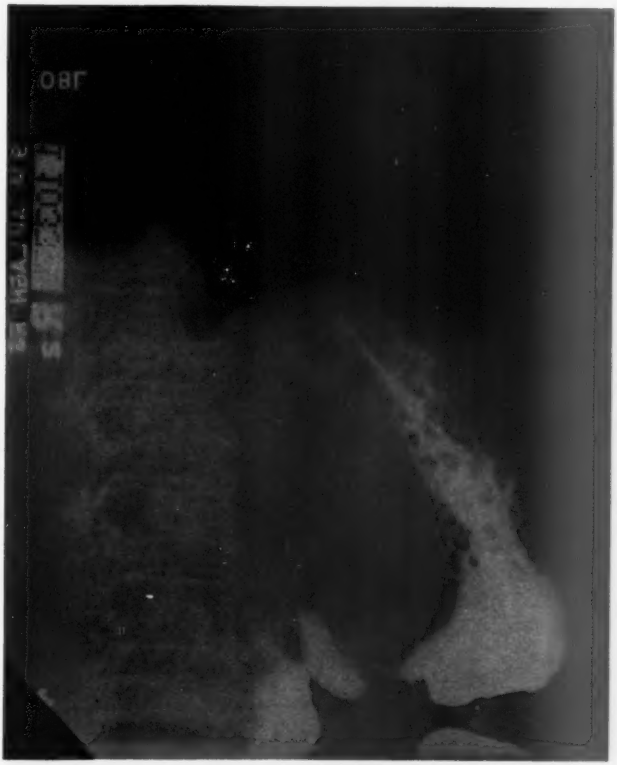

FIG. 1. Multiple polyposis.

Figure 2 shows a sessile type of benign adenomatous polyp of the stomach under low power. Figure 3 reveals a similar but pedunculated benign polyp. Figure 4 shows a greater magnification of an area in the pedunculated polyp.

Hardt and his co-workers [1] and Thompson and Oyster [2] found an age distribution of gastric polyps similar to ours. Hardt [1] and Wheelock [3] in separate series found a much higher incidence in males, ratios of from 2:1

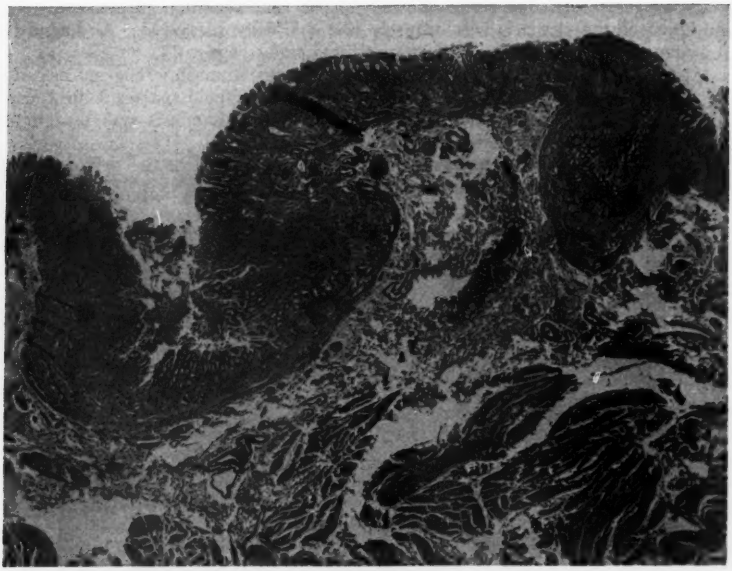

FIG. 2. Sessile polyp, low power.

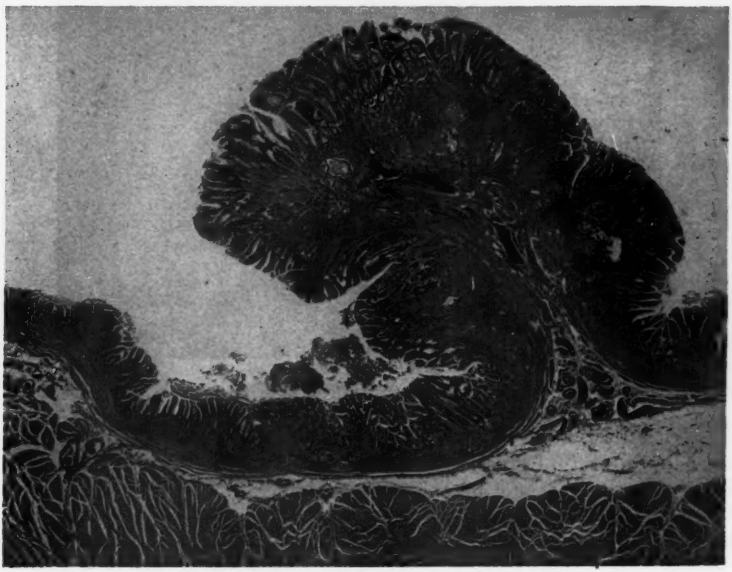

FIG. 3. Slightly pedunculated polyp, low power.

to 4:1. Carey and Hay [4] found the symptomatology not distinctive. Edwards and Brown [5] recommended surgical removal of benign polyps on the basis of possible malignant degeneration, although Carey and Hay stated that the theory of change from benign to malignant growth was not clearly established. In our own series we were unable to find any benign lesion which became malignant. Hardt reported x-rays negative in 40 per cent of the gastroscoped cases. In our series a similar ratio was obtained.

FIG. 4. High power of tip of pedunculated polyp.

SUMMARY

1. Thirty-two cases of benign gastric polyps have been studied.

2. Gastroscopy is superior to x-ray in the diagnosis of polyps, but the use of both procedures affords the best results.

3. The symptoms of gastric polyps are protean and none is pathognomonic, but abdominal discomfort, nausea and vomiting, and weight loss are common.

4. In no case did we encounter malignant degeneration of a benign gastric polyp.

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EFFECT OF OXYTETRACYCLINE THERAPY OF STREPTOCOCCAL SORE THROAT ON THE INCIDENCE OF ACUTE RHEUMATIC FEVER*

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Although penicillin, chlortetracycline, oxytetracycline and erythromycin have been shown to be effective in alleviating the symptoms of acute streptococcal disease, only penicillin and chlortetracycline therapy have been shown to reduce the incidence of rheumatic fever following such infections.[1-6] Since an important purpose of treatment is the prevention of complications, particularly rheumatic fever, it is necessary to evaluate the antirheumatic effect of each new drug employed in the therapy of streptococcal infections. In addition, the occurrence of reactions to the various drugs makes it essential that more than one form of therapy be available to the physician.

The present study is concerned with the evaluation of oxytetracycline † therapy of streptococcal respiratory infections. Data will be presented to show the effect of treatment on the streptococcal carrier rate, immunologic response of the host and the attack rate of rheumatic fever.

Methods and Description of Population

The methods employed in this study were similar to those previously reported.[5] Fourteen hundred and nine hospitalized airmen with acute exudative tonsillitis or pharyngitis were admitted to the study. With few exceptions, patients were excluded who gave a past history of rheumatic fever, presented signs of rheumatic heart disease or showed evidence of a

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† Oxytetracycline (Terramycin) was generously supplied by Dr. Gladys L. Hobby, Charles Pfizer and Company, New York.

complication at the time of initial examination. The patients were examined on admission to the study and approximately three weeks after the acute infection. A small group was examined again four weeks after admission. Historical information, physical examinations and laboratory studies were obtained in a standard fashion. The criteria for the diagnosis of acute rheumatic fever were those of Jones [7] with slight modifications.[8]

Selection of the patients for therapy with oxytetracycline or placebo was made by Air Force serial number except for 123 of the patients in Schedule I, who were selected by well shuffled decks of cards (table 1). In addition, these 123 patients, of whom 60 received oxytetracycline and 63 received placebo therapy, included only those who had been ill less than 30 hours

TABLE 1

Distribution of Patients Among the Three Treatment Schedules

	Oxytetracycline	Inclusive Dates	Number		Totals
			Controls	Treated	
I.	1 gm. stat 0.5 gm. q/6h×19 Total dose—10.5 gm. over a 5 day period	3/10/51– 3/19/51 3/29/51– 4/28/51	179	128	307
II.	0.5 gm. q.i.d.×20 Total dose—10 gm. over a 5 day period	5/13/52– 9/29/52	200	214	414
III.	0.5 gm. q/6h×20 Total dose—10 gm. over a 5 day period	8/13/51–11/18/51 12/ 8/51– 1/ 2/52 9/30/52– 1/ 4/53	317	371	688
	Totals		696	713	1,409*

* Sixteen additional patients who developed suppurative complications after admission (2 treated with oxytetracycline and 14 controls) received penicillin therapy and are excluded from the study. In addition, 2 patients who had rheumatic fever at the time they were admitted with exudative pharyngitis are excluded.

and whose total leukocyte count was 10,000 per cu. mm. or above.[2] All three treatment schedules were similar in that oxytetracycline was given over a five day period. The methods of administering oxytetracycline were altered to allow the use of the patients in other studies,[2, 8] and were not employed with the intent of evaluating different dosage regimens.

A large number of patients had non-streptococcal exudative pharyngitis, as indicated by the fact that group A streptococci were not isolated from the initial culture of the throat of 29% of the patients and 38% did not exhibit a leukocytosis. In order to exclude the majority of patients with non-streptococcal infections or inadequate follow-up studies, analyses of the data were limited to those patients who harbored group A streptococci at the time of admission and who were seen for a convalescent examination.

A total of 986 such patients was available, of which 506 received oxytetracycline and 480 served as controls. The distribution of these cases among the various treatment schedules is shown in table 2. That most of the illnesses in this group of 986 patients were caused by the group A streptococcus is further indicated by the presence of leukocytosis in the majority of patients and by the demonstration of a diagnostic increase in antistreptolysin "O" titers * in 71% of the untreated patients in Schedule I, 84% in Schedule II and 78% in Schedule III.

TABLE 2

Comparability of Groups of Patients Who Had Group A Streptococci Isolated from Initial Throat Culture and Who Were Seen for a Convalescent Examination

	Schedule I		Schedule II		Schedule III	
	Control	Treated	Control	Treated	Control	Treated
Total number of patients	152	112	127	147	201	247
Percentage with:						
Previous history of:						
Rheumatic fever	1.3	1.8	0.8	0.7	0.5	0.4
Heart murmur	0.0	0.0	1.6	2.7	2.0	4.5
Family history of rheumatic fever	10.5	8.0	8.7	4.8	7.0	11.7
Laboratory results on admission:						
Leukocyte count 12,000 or greater	73.7	77.7	64.6	58.5	72.1	60.3
Group A streptococci						
Type 1	15.8	27.7	3.1	2.7	1.0	2.0
5	16.4	7.1	7.1	6.1	4.0	3.2
6	7.2	7.1	3.9	2.7	2.0	1.2
14	49.3	48.2	21.3	24.5	13.4	15.4
19	0.0	0.0	3.1	2.0	35.8	42.1
30	0.0	0.0	42.5	35.4	13.4	8.9
Non-typable	2.6	2.7	7.9	9.5	12.9	11.3
Other types	8.7	7.2	11.1	17.1	17.5	15.9
Antistreptolysin—125 units or less	64.5	61.6	74.0	69.4	75.6	66.8
Onset of illness to beginning of treatment						
0–30 hr.	75.0	72.3	48.8	48.3	43.8	42.9
31–60 hr.	21.1	21.4	40.2	39.5	33.3	36.0
61–98 hr.	1.3	1.8	5.5	6.8	10.0	7.7
99 or greater	1.3	0.0	2.4	0.7	3.5	5.7
Unknown	1.3	4.5	3.1	4.7	9.4	7.7
Follow-up examination 21–34 days after onset	91.4	86.6	92.9	91.8	84.6	83.8

Included in table 2 are certain clinical and laboratory data obtained from the 986 patients at the time of admission to the study. The treated and control groups within each schedule appeared to be comparable, although there were certain differences among the schedules. Considerable variations in the serologic type of the infecting streptococcus occurred during the investigation. Therapy was instituted earlier and the total leukocyte counts were higher during Schedule I than in the other treatment groups.

* A change in antistreptolysin titer of two dilution increments or more is considered a diagnostic increase. Antistreptolysin "O" will subsequently be referred to as antistreptolysin or antibody.

This was a reflection of the different manner in which 123 patients of Schedule I were selected, as mentioned previously.

Results

Oxytetracycline was administered for five days to 506 patients with exudative tonsillitis or pharyngitis from whom group A streptococci were isolated prior to therapy. Three weeks later, 24% of the patients still harbored the infecting type of streptococcus (table 3). This represented a 55% reduction in the carrier rate as compared to the bacteriologic results in the control patients. Approximately 10% of the patients in the treated and control groups acquired a new serologic type of streptococcus by the third week of observation.

Table 3

Effect of Oxytetracycline on the Infecting Type of Group A Streptococci *

Treatment	Total Patients	Group A Streptococci at Convalescent Examination			
		Infecting Type		New Type	
		Number	Per Cent	Number	Per Cent
Control	473	253	53	54	11
Oxytetracycline	500	121	24	49	10

* Thirteen patients are excluded because the follow-up bacteriologic results were not available. Of those patients who were seen for two convalescent examinations, only the bacteriologic results of the first examination are included.

The average antistreptolysin responses of the treated and control patients are shown in table 4. Oxytetracycline therapy resulted in a 49% reduction in the average antistreptolysin response as compared to those patients who received no treatment. There was no significant difference between the

Table 4

Average Antistreptolysin Production According to Bacteriologic Results Three Weeks after Admission *

Results of Cultures at Time of Follow-up	Control		Treated	
	Total Patients	Average Antibody Response	Total Patients	Average Antibody Response
		Units		Units
Same type of streptococcus as isolated initially	242	184	119	147
No group A streptococci isolated	158	170	322	77
Different type of streptococcus than originally isolated	53	254	48	107
Totals	453	187	489	97

* Only patients who had paired sera are included.

TABLE 5

Average Increase of Antistreptolysin in Patients Who Had Group A Streptococci Isolated from the Initial Throat Culture and Who Were Seen for Two Convalescent Examinations *

Results of Follow-up Throat Cultures	Number of Patients	Average Unit Rise from Onset of Illness to Convalescent Examination	
		3 Weeks	4 Weeks
Control patients			
Negative at both examinations	16	189	170
Infecting organism isolated at one or both convalescent examinations	56	203	214
Treated patients			
Negative at both examinations	56	76	76
Infecting organism isolated at one or both convalescent examinations	34	128	197

* Includes only patients from whom initial and both convalescent sera were available.

various treatment schedules. Maximal inhibition of antibody was obtained in those treated patients whose follow-up culture showed no group A streptococci. If therapy was not sufficient to eliminate the organism, little inhibition of antibody was observed.

The control patients who acquired another serologic type of streptococcus during convalescence showed the greatest increase in antistreptolysin, probably due to the influence of two antigenic stimuli. The patients who received oxytetracycline and acquired a different type of streptococcus developed somewhat less antibody than those who harbored the infecting type at three weeks.

TABLE 6

Distribution of Nonsuppurative Complications during Study of Oxytetracycline *

Classification	Control	Treated	Total
Total patients observed	480	506	986
Total complications	26	17	43
Definite rheumatic fever	15	9	24
Possible rheumatic fever	4	3	7
Others† (joint symptoms or signs)	7	5	12

* No cases of acute glomerulonephritis were observed.
† Exclusive of first 2 categories. All symptoms in this classification occurred within four weeks of the onset of the observed infection.

The amount of antibody produced in the control group of patients was about the same in those who showed no streptococci in the culture of the oropharynx at the time of the convalescent examination as in those who still carried the infecting organism. This would indicate that the antigenic stimulus in the two groups was equal in spite of the persistence of the infecting organism in one group and the apparent absence of the organism in the other. The absence of streptococci in most of these untreated patients

TABLE 7

Nonsuppurative Sequelae Developing

Treatment Schedule	Case	Age	Exudative Tonsillitis					Throat Culture	Interval to RF (days)	Acute				
					Antistreptolysin					Admission		History		
			Treatment	WBC 1,000	Acute Titer	Conval. Titer	Tube Increase			Culture	ASL Titer	Family	Rheumatic Fever	Heart Murmur
I	331	21	0	16	62	159	4	A-1	2‡	A-1	200	0	0	0
	300	19	0	24	250	625	4	A-14	10	A-14	400	0	0	0
	265	27	0	13	40	200	7	A-5	13‡	A-5	200	0	0	0
	297	19	0	16	83	159	3	A-5	21	A-5	159	±	+	0
	295	20	0	13	100	125	1	A-14	26	A-14	250	0	0	0
	344	19	0	17	317	500	2	A-14	31	A-1	400	0	±	0
	330	19	+	18	159	200	2	A-14	2‡	0	200	0	±	0
	329	25	+	13	159	625	6	A-1	19	A-1	400	+	±	0
	335	21	+	15	100	200	4	A-14	46	A-14	200	0	+	0
	341	22	+	21	100	200	3	A-14	57	0	200	0	0	0
II	531	20	0	8	100	—	—	A-14	21	A-14	500	0	0	0
	548	20	0	9	83	159	3	A-30	24	A-30	250	0	±	+
	555	19	0	22	62	250	3	A-19	24	0	250	0	0	0
	552	27	+	4	100	100	0	A-12	31	A-12	125	0	0	0
	553	20	+	6	317	317	0	A-nt	64	0	500	0	0	0
III	551	17	0	23	125	200	2	A-14	3	A-14	200	0	0	0
	386	20	0	13	100	317	5	A-14	12	A-14	250	0	0	0
	561	20	0	18	159	250	2	A-19	24	A-19	317	0	0	0
	562	21	0	15	159	250	2	A-30	24	A-30	250	+	0	0
	573	24	0	10	83	125	4	A-19	27	0	250	0	0	0
	563	17	0	10	125	500	6	A-3	28	A-19	500	0	0	0
	408	20	0	13	100	200	3	A-5	31	0	125	0	0	0
	394	21	0	12	83	500	7	A-18	53	0	400	0	0	0
	577	19	0	19	200	500	4	A-19	78	0	317	0	0	0
	414	18	0	21	100	500	7	A-14	143	A-1	500	–	0	0
	734	—	+	6	317	317	0	A-19	8	A-19	317	±	0	0
	381	19	+	8	250	250	0	A-5	9	A-5	200	+	+	+
	993	—	+	15	62	100	2	A-19	27	0	100	0	0	0
	402	18	+	10	317	500	2	A-nt	32	0	500	0	0	0
	575	19	+	11	250	250	0	A-19	32	0	250	0	0	0
	533	19	+	8	200	250	1	A-14	203	0	200	0	0	0

Explanation—ASL: Antistreptolysin "O" titer. Family history: Rheumatic fever or rheumatic heart disease. Joints: P = pain; R = redness; T = tenderness; S = swelling; Mul. = multiple involvement of joints; Mig. = migrating involvement of joints. Heart: MS = mitral systolic murmur; MD = mitral diastolic; AD = aortic diastolic; * = murmur considered significant. Sed. rate: Maxi-

TABLE 7—*Continued*

during Study of Oxytetracycline Therapy

Rheumatic Fever													
Physical Examination										Laboratory			Remarks
Joints							Rash	Heart Murmur	Max. Temp.	Sed. Rate	EKG		
P	R	T	S	Mul.	Mig.					P-R (sec.)	Other	
0	0	0	0	0	0	0	MS	100.4	23	0.19	⊥1, 2, 3	Possible rheumatic fever.
+	0	+	0	+	+	0	MS,* MD, AD	99.8	42	0.39	0	
0	0	0	0	0	0	0	0	100.0	35	0.44	0	Acquired type 1 infection 15 days after onset of rheumatic fever. Fever and elevated sedimentation rate occurred at that time. Possible rheumatic fever.
+	+	+	0	+	+	0	MS*	100.2	48	0.22	0	
+	0	+	0	+	+	0	0	100.2	17	0.17	0	
+	0	+	0	+	+	0	0	100.4	43	0.41	0	Type 1 isolated two weeks before rheumatic admission.
0	0	0	0	0	0	0	MS	100.0	30	0.23	0	Abdominal pain.
+	0	0	0	+	+	0	MS*	100.6	34	0.30	0	One year previously had arthralgia and prolonged P-R interval.
+	+	+	+	+	+	+	MS	100.2	45	0.24	0	Type 14 infection two weeks before the observed pharyngitis. Treated with chlortetracycline.
+	+	+	+	+	+	+	MS*	104.6	42	0.23	0	
+	0	+	0	+	+	+	MS,* AS	102.2	38	0.19	0	
+	0	+	0	+	+	0	MS*	100.0	43	0.31	0	
+	0	+	0	+	+	0	MS*	100.6	50	0.21	0	Type 19 isolated on the second day of hospitalization for rheumatic fever.
+	0	+	+	0	0	0	MS	100.0	19	0.17	0	Abdominal pain. Possible rheumatic fever.
+	+	+	+	+	+	0	MS*	102.6	34	0.18	0	Suggestive serologic evidence of an intervening streptococcal illness.
0	0	0	0	+	+	0	MS*	101.0	24	0.17	0	Empyema of right maxillary sinus. Possible rheumatic fever.
+	0	+	0	+	+	0	MS,* MD	99.8	25	0.18	0	
+	0	+	+	+	+	0	MS*	101.2	34	0.20	0	
+	0	+	0	+	+	0	MS*	100.4	37	0.18	0	
+	0	+	+	+	+	0	MS*	101.2	52	0.16	0	Type 19 isolated on seventh hospital day of rheumatic admission.
+	0	+	0	+	+	0	0	100.2	6	0.16	0	Possible rheumatic fever.
+	+	+	+	+	+	+	MS*	103.6	47	0.17	0	Erythema marginatum.
+	0	+	0	+	+	0	0	100.4	16	0.16	0	No evidence of intervening illness.
+	0	+	+	+	+	0	MS*	104.4	52	0.19	0	Nine days before rheumatic admission was hospitalized with type 30 pharyngitis.
+	+	+	+	+	+	0	MS	102.2	36	0.22	0	
0	0	0	0	+	+	0	0	98.6	39	0.16	—	Possible rheumatic fever.
+	0	+	0	+	+	0	MS*, AD*, MD*	101.2	25	0.22	0	Developed subcutaneous nodules.
0	0	0	0	+	+	0	0	—	15	0.16	0	Possible rheumatic fever.
+	0	+	+	+	+	0	MS*	102.0	46	0.20	0	
+	0	+	0	+	+	+	MS*, AD	102.4	42	0.40	Bu. Br. Block	Admitted 5 days before rheumatic admission with type 1 exudative pharyngitis, treated with penicillin. Admitted 2 weeks before recorded illness with type 19 exudative pharyngitis, treated with chlortetracycline.
+	0	+	+	+	+	0	MS*	103.8	39	0.26	0	Admitted twice during intervening period with type 14 exudative pharyngitis. Treated with penicillin. Last illness 40 days before onset of rheumatic fever.

nal erythrocyte sedimentation rate, Wintrobe method. EKG: Maximal P-R interval recorded. ⊥: Indicates inversion of T-wave. ‡: Patients were being observed for another study.[8] Interval represents time between onset of pharyngitis and appearance of an abnormal EKG.

may be artificial, for it has been shown that, if frequent cultures are obtained, all untreated patients harbor the infecting streptococci three weeks after the illness.[8]

One hundred seven treated patients and 93 control patients during Schedule III were observed during the third and again during the fourth weeks of convalescence. In the control group 57% of the patients were found to harbor the infecting type of streptococcus at the time of the first convalescent examination, and at the second examination the infecting organism was isolated from an additional 12%. Thus, by means of one follow-up culture only 57% of the control patients were found to be carriers, but by an additional convalescent culture a total of 69% were shown to harbor the infecting streptococcus. Similar data were obtained in the treated patients, for although the organisms were isolated in 28% of patients at the time of the first convalescent examination, the additional results of the second follow-up culture increased the number of patients in whom the infecting organism was isolated to 34%.

Further changes in antibody production were noted in patients observed for four weeks (table 5). A marked rise in antibody occurred between the first and second follow-up examinations in the treated patients who remained carriers, indicating that continued antigenic stimulation was occurring in these individuals, whereas the average antibody titer remained unchanged in the treated patients in whom the organism had been eradicated.

Effect of Treatment on the Incidence of Rheumatic Fever

Post-streptococcal, nonsuppurative complications developed in 43 of the 986 patients included in the study. The severity of the complications varied from simple joint pains to classic attacks of acute rheumatic fever. The distribution of these complications between the treated and control groups is shown in table 6. Essential clinical and laboratory data are recorded in table 7.

A total of 31 patients developed an illness classified as definite or possible rheumatic fever and, of this group, 19 occurred in the control patients and 12 in patients who received oxytetracycline. There was no evidence that therapy was administered later in the course of the acute streptococcal illness in those patients who developed rheumatic fever than in the total number of patients who received therapy.

The intervals between the onset of the observed attack of pharyngitis and the onset of rheumatic symptoms varied from two to 143 days in the control patients and from two to 203 days in those who received oxytetracycline. Many of the rheumatic episodes may not have been directly related to the observed streptococcal infection, as evidence was obtained in some instances which indicated that a second untreated streptococcal infection occurred during the latent period. As shown in table 8, such intervening infections were most frequently observed in those patients whose

latent periods exceeded 35 days. Bacteriologic, serologic or historical evidence of a streptococcal infection occurring during the latent period was obtained in five of the seven rheumatic subjects who exhibited intervals exceeding 35 days. In contrast, evidence for intervening streptococcal infections was obtained in only three of the 24 patients who developed rheumatic fever within 35 days after the onset of the observed streptococcal illness. It is possible that therapy which merely suppressed the growth of the organisms resulted in a recurrent infection with the same streptococcus some time after therapy had been discontinued. In such instances the interval to the development of rheumatic fever might be prolonged. This sequence of events may have occurred in one patient (335) who was treated with oxytetracycline and who developed rheumatic fever 46 days later.

These data support previous experience [5, 6, 8] indicating that the observed streptococcal infection is usually directly related to the attack of rheumatic

TABLE 8

Occurrence of Streptococcal Infections during Interval between Observed Streptococcal Infection and Onset of Either Rheumatic Fever or Possible Rheumatic Fever

Interval to Rheumatic Fever	Number of Patients	Number of Patients with Evidence of Intervening Infection			
		Bacteriologic	Serologic	Historical	Total
1–35 days					
Control	16	2	0	0	2
Treated	8	1	0	1	1
Greater than 35 days					
Control	3	1	0	1	2
Treated	4	0	2	1	3

fever when the interval is less than 36 days. In the present study definite rheumatic fever occurred within 35 days in 12 cases of the control group of 480 patients, and in five of the 506 treated patients, representing a reduction in the attack rate from 2.94% in the control group to 0.99% in those who received therapy with oxytetracycline ($p = 0.07$).

EFFECT OF TREATMENT ON RECURRENT PHARYNGITIS AND SUPPURATIVE COMPLICATIONS

No re-admissions for pharyngitis occurred in the treated group during the first week following the onset of the streptococcal illness. After the first week of illness, however, re-admissions for recurrent streptococcal pharyngitis occurred more frequently in the patients treated with oxytetracycline than in the control group. During the second and third weeks of convalescence there were 14 admissions for pharyngitis in the treated group, of which 10 illnesses appeared to be caused by the original infecting organ-

ism (table 9). In contrast, there were three readmissions during the second and third weeks in the control patients, from one of whom the original infecting organism was isolated. Thus, re-admissions for streptococcal pharyngitis occurred more frequently in the treated patients and usually developed within a few weeks after therapy had been discontinued. Although some of these recurrent illnesses may have been due to re-acquisition of the same serologic type of streptococcus, it appears more likely that the original infecting organisms persisted in spite of treatment and caused the second infection.[6]

TABLE 9

Occurrence of Suppurative Complications and Recurrent Streptococcal Pharyngitis

	Number of Days from the Time of Admission to the Onset of the Complication				
	1–7	8–14	15–21	22 or Greater	Total
Recurrent pharyngitis:					
a) Due to original infecting organism					
Control	2	1	0	4	7
Treated	0	7	3	8	18
b) Due to a different group A streptococcus					
Control	0	1	1	3	5
Treated	0	2	2	18	22
Suppurative complications*					
Control	13†	0	0	1†	14
Treated	2	0	3‡	1†	6

* Peritonsillar abscesses unless indicated.
† One case of acute otitis media.
‡ Two cases of acute sinusitis.

Suppurative complications developed especially during the first week of hospitalization and occurred more frequently in the control patients (table 9).

DISCUSSION

In the selection of one of the various antibiotics for the treatment of patients with streptococcal pharyngitis, the following four factors should be considered: (1) the alleviation of symptoms associated with the acute illness; (2) the eradication of the streptococcus; (3) the prevention of suppurative complications, and (4) the prevention of the serious complications, acute rheumatic fever and acute glomerulonephritis. Several studies [1, 2, 4] have established the fact that penicillin, chlortetracycline, oxytetracycline and erythromycin all exert a beneficial effect on the clinical course of acute streptococcal tonsillitis and pharyngitis. None of these compounds is clearly superior in this regard.

The second factor, the elimination of group A streptococci from the oropharynx, has received little emphasis as being an important consideration

in the treatment of streptococcal diseases. It is important in relation to the public because the infected individual may spread the disease to others. The successful eradication of the streptococcus depends theoretically upon the total dosage and the duration of therapy. Actually, within certain broad limits, the total dose of antibiotic does not appear to be an important factor. Thus, doubling the dose of oxytetracycline from 5 gm. given over five days to 10 gm. administered for a similar period[8] did not alter the convalescent carrier rate of group A streptococci. Other studies[10] have shown that a single injection of 600,000 units of benzathine penicillin, a slowly absorbed compound, more effectively reduced the convalescent carrier rate than the daily injection of 600,000 units of aqueous procaine penicillin for five days.[2] This would indicate that the maintenance of effective concentrations of penicillin was more important than the total dose employed. Likewise, the duration of treatment with chlortetracycline appears to be important in relation to the elimination of group A streptococci, since therapy for six days was superior to treatment for four or five days.[6] There is inadequate information concerning the relationship of duration of erythromycin therapy to its ability to eradicate group A streptococci. In one study in which the convalescent carrier rate was markedly reduced,[4] treatment with erythromycin for 10 days was as effective as penicillin employed for a similar period of time. It is theoretically possible that the administration of oxytetracycline or chlortetracycline for 10 days may be equally as effective in eradicating streptococci as erythromycin and penicillin.

The preceding discussion of the relationship of duration of treatment to the elimination of the infecting streptococcus becomes even more important in view of recent studies, which have shown that eradication of the organisms is essential if rheumatic fever is to be prevented.[6, 8] Indeed, it is possible to judge the antirheumatic effect of various types of therapy of acute streptococcal infections by careful studies of the convalescent carrier rate. Further support of the reliability of the bacteriologic technics employed can be obtained by including studies of the antibody response of the host to the infection, since, if the organisms are eradicated, there is little antibody production.

It is difficult to compare the efficacy of the various antibiotics in the prevention of suppurative complications. Treatment with penicillin,[1, 2] oxytetracycline and chlortetracycline[1, 2, 6] decreases the incidence of otitis media, sinusitis and peritonsillar cellulitis. Inadequate therapy with these antibiotics results in recurrences of respiratory infections, presumably due to the failure to eradicate the infecting organism.

The fourth and most important factor in the treatment of streptococcal sore throat is the prevention of acute rheumatic fever and acute glomerulonephritis. Before compounds are accepted for use in the therapy of streptococcal disease, there should be adequate information concerning the thera-

peutic regimen required for the prevention of rheumatic fever and nephritis. Since the attack rate of these complications is low, large groups of patients must be treated to obtain such information. Of the three drugs thus far evaluated, penicillin reduced the attack rate of rheumatic fever by 91%,[5] chlortetracycline by 74%[6] and oxytetracycline by 66%; however, it must be emphasized that the total dose and duration of treatment in each study were different. Although little is known about the ability of these antibiotics to prevent acute glomerulonephritis, data to be presented elsewhere indicate that penicillin therapy of streptococcal pharyngitis will decrease the incidence of this complication.[9]

In summary, until further data are available it is recommended that penicillin, administered so that effective concentrations are maintained for at least 10 days, be used in the treatment of streptococcal infections. This may be accomplished by the single injection of 600,000 to 900,000 units of benzathine penicillin or by the oral administration of 250,000 to 500,000 units of penicillin twice daily for 10 days. Erythromycin, chlortetracycline and oxytetracycline should be reserved for those patients who are unable to tolerate penicillin and, if they are employed, should be administered for at least 10 days.

Summary

The results of treatment of 506 patients with streptococcal exudative pharyngitis with oxytetracycline administered for five days is presented. Four hundred eighty patients who received no specific therapy served as controls.

In the dosages employed, oxytetracycline reduced the convalescent streptococcal carrier rate 55% as compared to the control group. In addition, the average antistreptolysin response in the treated patients was 49% less than that observed in the control patients. Maximal inhibition of antibody production occurred in the treated patients in whom the infecting organism was eliminated.

Recurrent pharyngitis occurred more frequently in the treated group, particularly in those patients who remained carriers. The second clinical illness usually developed within two to three weeks after therapy had been discontinued. Suppurative complications were of infrequent occurrence in both groups.

Rheumatic fever developed within 35 days after the onset of the streptococcal infection in 12 patients in the control group and in five patients in the group treated with oxytetracycline. The attack rate was reduced, therefore, from 2.94% in the control group to 0.99% by therapy with oxytetracycline ($p = 0.07$).

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THE MANAGEMENT OF REFRACTORY EDEMA IN HEART FAILURE*

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THIS report is concerned with edema which is refractory to usual methods of treatment. Most patients with heart failure eventually develop edema. Often this is an early manifestation. Many factors contribute to the retention of salts and water which produce an excess of extracellular fluid. In some respects the edema of heart failure may be considered only a symptom, indirectly reflecting the derangement of hemodynamics which characterize this state. From evidence which has been accumulated from many sources, it is now generally accepted that under certain circumstances the expansion of extracellular fluid, per se, may contribute to the failure of the heart, thus completing a vicious cycle. From knowledge of these factors, much of our clinical estimation of cardiac compensation is based on the presence or absence of edema in the patient with congestive failure.

In the early stages of congestive heart failure most patients can be maintained edema-free by such measures as limited activity, the use of digitalis, a low salt diet, or occasional mercurial diuretic injections. From recent studies [1] it has been estimated that in the early stages 90% of patients can be managed by even the casual combination of any of these measures. Of the remaining 10% of patients, 90% have been estimated to respond to a regimen including mercurial diuretics two or three times a week. This leaves the small proportion of 1% of total patients with congestive heart failure who present a problem of refractory edema when first seen. Ultimately, however, in the natural history of congestive heart failure, most patients progress to the point at which they require more vigorous application of these therapeutic measures, often including the daily injection of mercurial diuretics. As the disease progresses most patients develop a relatively refractory state. Great interest has been shown in various therapeutic maneuvers which might modify the course of this refractory edema. Unusual combinations of therapeutic agents have been recommended but do not often reverse the course of this state. Cation exchange resins have been of little value in the refractory patients in our experience.

Transient refractory phases of edema in heart failure may be produced by complicating disease of many types. Hypermetabolism of any cause,

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such as hyperthyroidism, infection or inflammation, may contribute to this state. Primary hepatic or renal disease often poses a serious problem. Constrictive pericarditis, pericardial effusion or specific myocarditis, to name a few of the less common conditions, may be important contributing factors. It should be emphasized that an orderly evaluation of the therapeutic regimen is a first requirement in determining the cause of refractory failure. It has been our experience that the most effective application of the usual therapeutic measures will eliminate the apparently refractory state in a large number of patients. After these considerations the great majority of patients with refractory edema due to heart failure are those who have progressed in the natural history of their disease to a point at which the defect producing salt and water retention cannot be modified by the usual therapeutic measures.

There has been much discussion of electrolyte imbalance as a cause of refractory heart failure. In our experience electrolyte imbalance of any type is rarely a cause of refractory failure. In most instances electrolyte

TABLE 1

This presents certain alterations in body fluids and chemical characteristics of the blood in congestive heart failure at admission and immediately following diuresis. The common finding is italicized in each instance.

	At Admission	With Diuresis
Extracellular fluid (blood volume)	*High*	To normal
Intracellular fluid	*High* to normal	To normal
Plasma sodium	*Normal* to low	*Normal* to low
Plasma chloride	*Normal* to high	*Normal* to *low*
Plasma carbon dioxide	*Normal* to low	*Normal* to *high*
Plasma potassium	*Normal*	*Normal*
Blood urea nitrogen	High to *normal*	*Normal* or slightly high
pH	Low, *normal* or high	Normal

imbalance occurs *because* of the presence of refractory failure and the application of vigorous therapeutic measures in an attempt to modify this state. The two most common types of electrolyte imbalance which have been described as causes of refractory failure are (1) hyponatremia in association with hypochloremia, the "low salt syndrome" and (2) hypochloremic alkalosis. The former can be produced in many patients with refractory edema by the application of very vigorous therapeutic measures such as extreme salt restriction, resin therapy or protracted daily mercurial injections. Dilution of extracellular fluid electrolytes by the retention of excess water contributes to the development of this hypoelectrolytemia in many patients. In our experience it is very uncommon to observe a diuresis following the restoration of normal plasma electrolyte concentrations in this group of patients. The latter, hypochloremic alkalosis, has been shown occasionally to be the cause of the refractory state of edema in heart failure. It should be pointed out that some degree of decrease of the plasma chloride level is a common observation during diuresis in heart failure. Table 1 demonstrates some of the common alterations in body fluids and chemical charac-

teristics of the blood in congestive heart failure before and after diuresis. In studies which are to be reported,[2] in which daily mercurial diuretics were administered, an average decrease of plasma chloride electrolyte concentration of 10 mEq. per liter occurred at the end of a period of six days, with an average weight loss of 24 pounds. This was observed in association with an average decrease of plasma sodium of 5 mEq. As a result, the average change of carbon dioxide combining power was an increase of 5 mmol. per liter during the same period of time. If plasma electrolyte concentrations were normal initially, as they are in the majority of patients, the level of plasma chloride concentration at the end of diuresis was slightly below normal or remained within normal limits. In occasional patients, unpredictable and markedly disproportionate falls of plasma chloride concentrations may be seen. In some patients this occurs prior to the attainment of optimal body weight. Studies in this group of patients by Schwartz [3] and others have indicated that, with the hypochloremic alkalosis which occurs, a relative loss of responsiveness to mercurial diuretics may be observed. Responsiveness to mercurial diuretics recurred with the restoration of plasma chloride levels to normal.

In our laboratory most patients with refractory edema due to heart failure have normal plasma electrolyte concentrations prior to vigorous therapy. Because of this fact, in most patients it has not been possible for us to attribute the refractory state to electrolyte imbalance. Studies on the mechanism of mercurial diuresis have suggested that mercurial agents act as diuretics by the blockage of chloride reabsorption. In experiments in dogs [4] it has been demonstrated that presentation of a high renal chloride load potentiates the mercurial diuretic effect. Reasoning from this, and from observations that hypochloremia occasionally produces the refractory state, we decided to determine the effect of the production of hyperchloremia in patients with normal plasma chloride levels unresponsive to mercurial diuretics. The production of a hyperchloremia with maintenance of a normal plasma sodium concentration produces acidosis—a hyperchloremic acidosis.

Hyperchloremia of significant degree has been difficult to produce because agents which may be utilized have been poorly tolerated in sufficient amounts. Ammonium chloride in many respects is the ideal agent, but amounts sufficient to produce significant hyperchloremia are not well tolerated.

Recently a sulfonamide derivative, acetazoleamide (also known as carbonic anhydrase inhibitor 6063 and by the proprietary name Diamox), has been developed which specifically inhibits carbonic anhydrase at various sites in the body. Carbonic anhydrase is an enzyme which catalyzes the conversion of carbon dioxide and water to carbonic acid in the renal tubular cells. The dissociation of this carbonic acid makes hydrogen ion available for substitution for sodium ion in the tubular urine, and for the production of ammonium ions. When carbonic anhydrase is inhibited by Diamox administration, increased amounts of sodium and potassium bi-

carbonate are excreted in the urine, and there is a decreased excretion of ammonium ion. As a result an alkaline urine is excreted, and a hyperchloremic acidosis is produced in the plasma. A number of clinical applications for Diamox have been introduced, one of which is its use as an oral diuretic agent. Friedberg and Halpern [5] and Belsky [6] have demonstrated it efficacy in the removal of edema fluid in patients with congestive heart failure.

In our experience, in patients with edema due to refractory heart failure, no significant diuresis has resulted from the use of Diamox alone. A hyperchloremic acidosis of moderate degree has been produced irrespective of diuretic response. Following cessation of Diamox therapy, in the setting of hyperchloremic acidosis, restoration of responsiveness to mercurial diuretics has been observed in some patients. However, the moderate hyperchloremic acidosis produced by Diamox is often of insufficient magnitude to restore adequately responsiveness to mercurial diuretics. The hyperchloremia and acidosis may be potentiated by the concomitant or consecutive administration of ammonium chloride in as large amounts as tolerated, usually 8 to 10 gm. daily. By this means a hyperchloremic acidosis with plasma chloride levels as high as 129 mEq. per liter and plasma pH as low as 7.14 has been produced. No untoward effects of either the hyperchloremia or the acidosis have been observed in this study. In the setting of a sufficient degree of hyperchloremic acidosis, all patients with refractory edema whom we have studied have then responded to mercurial diuretics by diuresis to the desired body weight. In many instances the state of congestive failure has been markedly improved by removal of edema fluid in this manner.

Methods

Six patients during nine hospital courses with intractable edema due to heart disease were selected for study. All the patients were on a stable regimen including bed-rest, digitalis, a special low salt diet and 2.0 c.c. of Mercuhydrin intramuscularly daily. In no case was there complicating disease such as infection, pulmonary infarction or thyrotoxicosis. Observations were made of the clinical state of the patient, fluid balance, plasma pH, plasma and urine electrolyte concentrations and daily weights. Body weights were determined daily on bed scales. Plasma sodium and potassium were determined on a Perkin-Elmer, Model 52-A flame photometer using a lithium internal standard. Plasma chlorides were determined by the method of Schales and Schales, as modified by Summerson. pH was determined on a Cambridge Research pH meter using a temperature correction of 0.0147 for each degree centigrade to correct values to body temperature.

Results

In those patients with edema on a strict cardiac regimen unresponsive to daily mercurial diuretics, we found Diamox to be ineffective as a diuretic

agent. Diamox produced a fall in plasma pH and plasma carbon dioxide and a rise in plasma chloride concentration. Plasma sodium and potassium concentrations remained within normal limits. Chloride excretion in the urine decreased to low levels; sodium and potassium excretion increased slightly in most patients. In all patients with intractable heart failure, irrespective of diuretic response, a hyperchloremic acidosis resulted. The addition of ammonium chloride enhanced the hyperchloremic acidosis produced by Diamox alone.

The following observations were made when mercurial diuretics were administered. In the refractory phase, mercurial administration resulted in no change in the normal plasma electrolyte pattern, and an insignificant increase in the urinary chloride and sodium excretion. Following production of a hyperchloremic acidosis, a diuretic response to mercurial agents occurred in all patients. The urine during diuresis contained large amounts of sodium and chloride. Chloride exceeded sodium excretion in all instances. Blood plasma levels of pH, carbon dioxide and chloride tended to return to within normal limits. As the normal electrolyte pattern recurred, decreased responsiveness to mercurial diuretics was observed even though edema persisted. When ammonium chloride was administered with Mercuhydrin, to replace the chloride loss in the urine during diuresis, thereby maintaining the hyperchloremia, a sustained daily diuretic response could be achieved with mercurial administration.

Maximal response to Mercuhydrin occurred in all cases 48 hours after the last day on which Diamox was given. When Diamox and Mercuhydrin were administered on the same day, the optimal diuretic response to Mercuhydrin did not occur.

Studies on two patients during three hospital admissions are illustrated in the following case reports.

Case Reports

Case 1 (Course 1). A 34 year old white female with cardiac decompensation due to rheumatic heart disease had had marked edema and intermittent ascites for three years prior to admission. She had been followed in the cardiac clinic since her last hospital admission on a regimen of restricted activity, salt-poor diet and digitalis, and for the two months prior to the present admission had been receiving Mercuhydrin, 2 c.c. intramuscularly daily, and ammonium chloride, 6 gm. daily four times a week. Progressive decompensation resulting in anasarca led to her re-admission. At this time she exhibited marked dyspnea and orthopnea, 4 plus edema and ascites. The venous pressure was 220 mm. saline. Plasma electrolyte concentrations were normal. The nonprotein nitrogen was 31 mg. per cent.

A strict cardiac regimen on the ward, including Mercuhydrin injections daily for 10 days, resulted in only a one pound weight loss. The urinary output averaged 1,700 c.c. daily (approximating fluid intake minus insensible loss), with low urinary concentrations of sodium and chloride. Plasma electrolyte values remained within normal limits. The periods of study are illustrated in figure 1.

Following this base-line period, Mercuhydrin administration was discontinued and she was given Diamox daily for three days. A four pound weight loss occurred on the first day, no weight loss on the second, and a weight gain on the third day. The

urinary output averaged 1,800 c.c. There was a slight sodium diuresis the first day, with less excreted the next two days; the chloride excretion decreased to negligible levels. A moderate hyperchloremia was produced. The plasma chloride rose 15 mEq. to 116 mEq. per liter; the carbon dioxide combining power fell 6 mmol. to 22 mmol. per liter. The pH decreased slightly, from 7.35 to 7.31.

Administration of Mercuhydrin daily for three days in this setting did not produce a diuresis. The patient lost only three pounds. The urinary output averaged

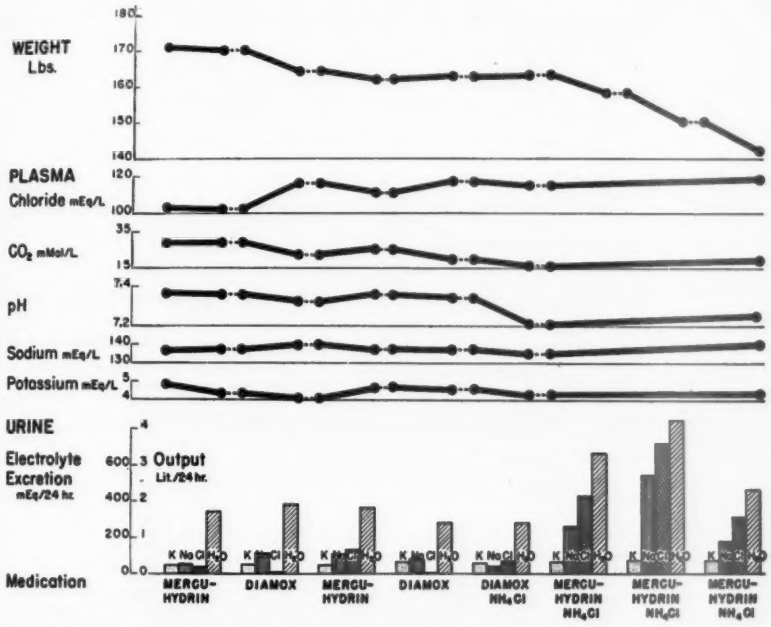

FIG. 1. *Case 1, Course 1.* This figure illustrates the first course of observation. On the ordinate are listed the body weight, plasma sodium, potassium, chloride and carbon dioxide concentrations, plasma pH, urine sodium, potassium and chloride excretion and total urinary output for 24 hours. On the abscissa are listed the medications and numbers of days each medication or combination of medications was given. From beginning to end of the charted course the observation period is continuous. The bars represent the average daily excretion of potassium, sodium, chloride and urine during the individual treatment periods.

1,700 c.c., with a slight increase in chloride excretion. The plasma chloride concentration decreased to 111 mEq. per liter; carbon dioxide combining power increased to 25 mmol. per liter; the pH returned to 7.35.

Mercuhydrin administration was discontinued and Diamox was again given for three days. During this time the patient gained one pound. Urine output averaged 1,500 c.c. a day, with low chloride concentration. A hyperchloremia was again produced, with a chloride concentration of 117 mEq. per liter and a carbon dioxide combining power of 20 mmol. per liter. The pH decreased only to 7.33 from 7.35.

During the next three days, 10 gm. of ammonium chloride in divided doses were given with Diamox. A weight gain of one pound occurred. Urinary output aver-

aged 1,500 c.c. a day. An increased chloride excretion occurred in comparison with amounts excreted after Diamox alone. A moderately severe acidosis was produced in association with the hyperchloremia. The plasma chloride concentration was 115 mEq. per liter; the carbon dioxide combining power was 16 mmol. per liter; the pH decreased to 7.20.

In this setting of hyperchloremic acidosis, administration of 2 c.c. of Mercuhydrin intramuscularly for five days in combination with ammonium chloride, 10 gm. daily, resulted in a sustained diuresis with a 25 pound weight loss during this period. The maximal diuresis occurred the second day (48 hours after the last dose of Diamox was

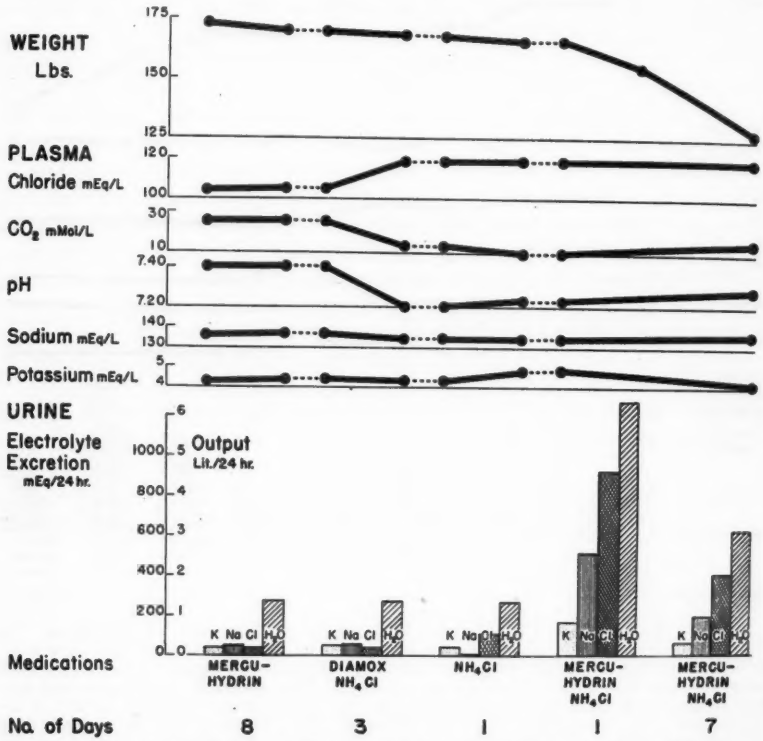

FIG. 2. *Case 1, Course 2.* This represents a second course of observation.

given), on which the urinary output was 4,200 c.c., with an eight pound weight loss. Urinary output averaged 3,100 c.c. daily, with markedly increased sodium and chloride concentration, chloride exceeding sodium.

A hyperchloremic acidosis was still present at the end of the five day period. The patient was markedly improved. Ascites and peripheral edema were no longer present. The venous pressure at this time was 105 mm. saline. She was discharged for ambulatory care.

Case 1 (Course 2). The patient whose first course of treatment is described above returned to the hospital three weeks later. She had failed to adhere to the salt-

poor diet and restricted activity program. She was dyspneic and orthopneic and had marked anasarca. The venous pressure was 230 mm. saline. Plasma electrolyte concentrations were within normal limits. The nonprotein nitrogen was 35 mg. per cent.

A cardiac treatment regimen including mercurial diuretic administration daily for eight days resulted in no clinical improvement. During this eight day period she lost only two pounds, edema and ascites persisting. At the end of this period the plasma urinary electrolyte pattern remained within normal limits. Figure 2 illustrates the plasma and urinary electrolyte and weight changes during the period of treatment described below. Mercuhydrin was discontinued. Diamox and ammonium chloride were

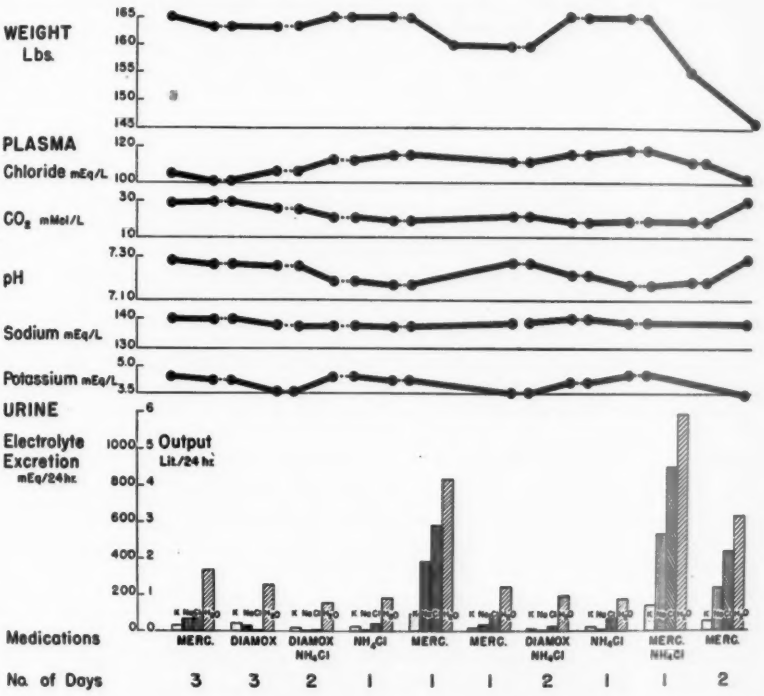

FIG. 3. *Case 2.* This represents the course of observation.

then administered for two days, and ammonium chloride was given alone the following day. The desired hyperchloremic acidosis was produced. The plasma chloride concentration was 119 mEq. per liter; the plasma carbon dioxide combining power was 15 mmol. per liter; the plasma pH decreased from 7.44 to 7.20. During this three day period the patient lost only two pounds and was clinically unchanged.

In the setting of this hyperchloremic acidosis, Mercuhydrin was administered daily for eight days. Ammonium chloride was also given to maintain the hyperchloremia. The first injection of Mercuhydrin, given 48 hours after Diamox was discontinued, resulted in a 6,400 c.c. urinary output and a 10 pound weight loss. The urinary chloride content was 935 mEq. and the sodium 715 mEq. The patient continued to respond to Mercuhydrin during the next seven days and lost 40 more pounds.

In the setting of a hyperchloremic acidosis, eight days of mercurial diuretic administration produced a 50 pound weight loss. During the base-line period, when the plasma electrolyte pattern was normal, mercurial diuretic administration for a similar period had produced only a two pound weight loss.

Case 2. A 52 year old Negro male with rheumatic heart disease for 10 years and increasing cardiac decompensation for the four years prior to admission was admitted to the hospital in severe congestive heart failure with anasarca. During the first month in the hospital a regimen of digitalization, bed-rest and a salt-poor diet, and the administration of a mercurial diuretic daily, resulted in no clinical improvement and no weight loss. Figure 3 illustrates the plasma and urinary electrolyte changes for each period of treatment described below. Mercuhydrin was discontinued. He was then given Diamox daily for five days, with ammonium chloride added on the fourth and fifth days. On the following day ammonium chloride only was given. During this six day period he gained two pounds. A hyperchloremic acidosis was produced. The plasma chloride concentration was 115 mEq. per liter; the carbon dioxide combining power was 19 mmol. per liter; the plasma pH decreased from 7.26 to 7.15.

In the setting of this hyperchloremic acidosis, Mercuhydrin was administered daily for two days. The first day the patient put out 4.5 L. of urine with high chloride and sodium content (590 mEq. of chloride, 385 mEq. of sodium); he lost five pounds. The second day no diuresis or weight loss occurred. The plasma chloride and carbon dioxide combining power had both returned toward normal and the plasma pH had risen to 7.26, the level prior to Diamox and ammonium chloride administration.

Then Diamox and ammonium chloride were given daily for two days, followed by ammonium chloride alone for one day. During this three day period, in which the patient regained the five pounds he had lost, the desired hyperchloremic acidosis was obtained. The plasma chloride concentration was 116 mEq. per liter; the plasma carbon dioxide combining power was 18 mmol. per liter; the plasma pH was 7.14.

Mercuhydrin was administered in the setting of this hyperchloremic acidosis. Ammonium chloride was also given the first day to maintain the hyperchloremia. A diuresis of 6 L. occurred in the first 24 hours; the urine contained 900 mEq. of chloride and 550 mEq. of sodium. The patient lost 10 pounds. Mercuhydrin was given on each of the next two days and the patient continued to diurese, losing 10 more pounds. At the end of this period the plasma electrolyte pattern had returned to within normal limits. The patient was symptomatically much improved, and was at desired weight after his 20 pound weight loss. Venous hypertension was no longer evident.

In every instance in which this plan of treatment has been tried it has been possible to produce a diuresis. Table 2 presents data from the nine courses of study in six patients.* The data are divided into two groups: when refractory, and later after responsiveness had been restored by the technic described previously. It should be noted that plasma electrolyte concentrations were essentially normal when the patients were refractory.

* Since this paper was presented further experience has been acquired in the use of this treatment regimen for refractory edema in heart failure. In the first 20 patients studied diureses have occurred with return of body weights to satisfactory levels in all but three patients. One of these patients died before an adequate diuresis could be accomplished. In another patient the regimen was interrupted by the necessity of an operative procedure. In the third patient a satisfactory diuresis did not occur even though a marked hyperchloremic acidosis was produced. This patient had advanced aortic stenosis and died soon after this treatment failure.

We continue to observe that untoward reactions are not produced by a moderate hyperchloremic acidosis. *However, as should be expected, symptomatic acidosis may result from prolonged and vigorous application of this regimen if close and frequent clinical and laboratory observations are not made.*

TABLE 2

This table compares body weight, plasma and urinary characteristics in individual patients on typical refractory and responsive days. In each instance 2.0 c.c. of Mercuhydrin were administered. In every case the responsive day data are those obtained 48 hours after the last day of Diamox administration.

			E. B.	E. B.	H. A.	S. B.	S. B.	G. B.	T. J.	T. J.	M. R.
Refractory	Plasma	Na mEq./L.	137	136	137	139	137	132	137	137	137
		K mEq./L.	4.8	4.3	4.3	3.5	3.7	4.5	4.6	4.6	4.4
		pH	7.36	7.42	7.36	7.41	7.38	7.35	7.28	7.28	7.42
		CO_2 mmol./L.	28	29	29	29	27	31	29	29	29
		Cl mEq./L.	103	104	105	102	103	107	105	105	105
	Urine	Vol. c.c./24 hr.	1500	1400	550	640	400	1000	1850	1250	1150
		Na mEq./24 hr.	60	50	40	5	5	18	81	37	7
		Cl mEq./24 hr.	45	42	27	1	6	52	99	107	25
	Wt. Change in Lbs.		0	0	+2	0	+1	+2	+1	0	+3
Responsive	Plasma	Na mEq./L.	137	134	137	139	138	135	136	136	145
		K mEq./L.	4.5	4.8	4.0	4.3	3.7	3.3	4.4	4.7	4.3
		pH	7.21	7.23	7.24	7.25	7.24	—	7.15	7.14	7.16
		CO_2 mmol./L.	16	13	21	21	16	19	19	19	17
		Cl mEq./L.	115	119	111	118	114	117	115	116	119
	Urine	Vol. c.c./24 hr.	4200	6400	2400	3500	2000	3300	4200	6000	2400
		Na mEq./24 hr.	542	530	370	296	140	168	385	550	175
		Cl mEq./24 hr.	715	935	350	463	300	425	590	900	320
	Wt. Change in Lbs.		−7	−10	−5	−5	−4	−4	−6	−10	−4

Injection of 2.0 c.c. of Mercuhydrin was associated with no weight loss or with a weight gain. The urine contained only small amounts of sodium and chloride. After production of the hyperchloremic acidosis, as shown in the lower grouping, injection of Mercuhydrin resulted in a marked diuresis, with weight losses of four to 10 pounds in 24 hours. The urine contained large amounts of sodium and chloride. It should be noted that in each instance the data for the responsive days represent observations on the second day following cessation of Diamox administration. In each instance when Diamox and Mercuhydrin were administered on the same day, or when Mercuhydrin was administered on the day immediately following Diamox therapy, maximal diuresis was not observed. Maximal diuresis with Mercuhydrin was observed to occur in every course in the setting of hyperchloremic acidosis on the second day following cessation of Diamox administration.

CONCLUSIONS

1. In our experience most patients with refractory edema do not have electrolyte imbalance prior to vigorous treatment.

2. In this study, in nine episodes of refractory edema due to congestive heart failure, restoration of responsiveness to mercurial diuretics was accomplished by the production of a hyperchloremic acidosis.

3. Diamox, or a combination of Diamox and ammonium chloride, was used to produce this hyperchloremic acidosis. No untoward effects of either the hyperchloremia or acidosis were observed in this study.

4. In the patients who are unresponsive to mercurial diuretics, Diamox is ineffective as a diuretic agent. However, a moderate hyperchloremic acidosis is produced by Diamox irrespective of diuretic response.

5. When Diamox and Mercuhydrin are administered on the same day, optimal diuretic response does not occur. Maximal diuresis with Mercuhydrin occurred the second day after Diamox was discontinued.

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THE ROLE OF HYPERTENSION IN THE ETIOLOGY AND PROGNOSIS OF CORONARY OCCLUSION *

By Louis H. Sigler, M.D., F.A.C.P., *Brooklyn, N. Y.*

The question as to whether hypertension plays a part in the etiology and prognosis of coronary occlusion has not as yet been definitely answered. Some authors [1, 2, 3] believe that hypertension is etiologically related to coronary occlusion. Master and co-workers [4] at first felt the same, but later Master [5] changed his opinion.

If we compare the percentage of normotensive and hypertensive cases who develop coronary occlusion as reported by various authors, we find that it varies markedly and its statistical value is therefore questionable. Thus, Howard [6] found 28% of his cases of coronary occlusion had hypertension. Conner and Holt,[7] 33.9%; White and Bland,[8] 34%; Mintz and Katz,[9] 35.9%; Levine and Brown,[1] 40%; Parkinson and Bedford,[10] 49%; Bean,[11] 49.3%; Rosenbaum and Levine,[3] 57%; Rathe,[12] 63%; Fisher and Zuckerman,[13] 65.5%; and Allan,[2] 76%.

As to the effect of hypertension on the prognosis of coronary occlusion, some of the authors mentioned above feel that hypertension decreases longevity after coronary occlusion. Donald [14] believes that the immediate prognosis of coronary occlusion is better in the presence of hypertension but that the ultimate prognosis is much worse. Palmer [15] found that hypertension makes the prognosis less favorable. Gross and Engleberg [16] found no effect on the longevity.

To help, if possible, to determine whether hypertension affects the incidence of coronary occlusion and whether it alters the prognosis, I reviewed a series of 1,160 cases of coronary occlusion, with and without hypertension, observed over a period of years. This paper is a report of my findings.

Material and Methods of Study

The 1,160 patients were part of a series of 1,700 cases, previously reported,[17] dealing with the general prognosis of angina pectoris and coronary occlusion. Each patient selected for the present study had had many blood pressure determinations over the years of observation, both before and after the onset of coronary occlusion. Inasmuch as blood pressure readings may show considerable spontaneous fluctuations,[18] the highest blood pressure levels in each case were used for classification. Those patients with normal blood pressure but without any knowledge of the preëxisting blood pressures have not been included in this series. Also, a few cases with aortic insufficiency were excluded because of blood pressure changes due to the lesion.

* Received for publication August 16, 1954.

The question as to what constitutes the upper limits of normal blood pressure has not as yet been definitely answered. From recent statistical studies [20, 21] it appears that as age advances the blood pressure levels rise progressively to far above the currently accepted upper normal levels, even in individuals who show no demonstrable organic disease. Upper limits as high as 190 systolic and 110 diastolic at 60 to 64 years of age have been considered normal, inasmuch as the individuals were apparently normal. For this reason I did not classify our patients into normal and hypertensive groups, but into divisions with designated range of blood pressure in each, as follows: Group I, systolic up to 140, diastolic up to 90; Group II, systolic 141–160, diastolic 91–100; Group III, systolic 161–200, diastolic 101–110; and Group IV, systolic above 200, diastolic above 110. In the last group a few cases had systolic blood pressure running as high as 300 and diastolic as high as 170, although in most cases the range of blood pressure was systolic 230 to 260, and diastolic 130 to 150.

The determinations included the ages in decades when the first attack of coronary occlusion occurred in each blood pressure group in the males and females; the average longevity following the first attack of coronary occlusion, and the length of survival of more than one year, five years and 10 years following the first attack of occlusion. In those cases where the blood pressures were above the currently accepted upper normal limits of 140 systolic and 90 diastolic, the duration of the higher pressures, as far as could be estimated from the histories and from the length of observation, was from three to 20 years. In general, the higher blood pressures were of longer duration and showed a progressive rise over the years of follow-up.

Observations

The 1,160 patients who had had at least one attack of coronary occlusion consisted of 946 males and 214 females. The proportion of males to females was thus about 4.4 : 1. Of these, 79.4% of the females and 48.9% of the males had blood pressures which are at present considered to be above normal levels. In other words, percentage-wise, hypertension was about twice as frequent in the females as in the males in this series. At the time of compilation of this report, 797 patients were still alive and 363 had died.

Age at First Attack of Coronary Occlusion: Table 1 shows the ages in decades when the first attack of coronary occlusion occurred in males and females in the various blood pressure groups.

It will be observed that coronary occlusion begins to appear earlier in life in the males than in the females in this series. It reaches a fastigium between 50 and 59 years in males and between 60 and 69 years in females.

If the blood pressure in Group I only is taken as normal, we find that 51.1% of the males and 20.6% of the females in the combined ages who had had an attack of coronary occlusion had normal blood pressure. If Group II is also considered within the normal range, 78.7% males and

42.5% females in the combined age groups who had had an attack of coronary occlusion had blood pressures within normal range, while 21.2% males and 57.5% females fell within the hypertensive group.

Between the ages of 20 and 29 there were five cases of coronary occlusion, all in males with perfectly normal blood pressure. Between 30 and 39 years there were only 60 males and only seven females who had had coronary occlusion. The greatest percentage of cases of coronary occlusion in males here is in the blood pressure Group I; the percentage is less in Group II, still less in Group III, and least in Group IV. In females, the number of cases is too small for comparison. As age progresses the incidence of both coronary occlusion and hypertension increases, but the increase of the two conditions is not proportionate. Thus, in the males up to and including 59 years of age there is a progressive rise in the per-

TABLE 1

Age, in Decades, at First Attack of Coronary Occlusion among Normotensive and Hypertensive Males and Females

Ages	Males										Females									
	Total Cases		Group I		Group II		Group III		Group IV		Total Cases		Group I		Group II		Group III		Group IV	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
All ages	946	100.	484	51.1	261	27.6	127	13.4	74	7.8	214	100.	44	20.6	47	21.9	62	28.9	61	28.5
20–29	5	0.5	5	100.	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
30–39	60	6.4	36	60.0	15	25.0	8	13.3	1	1.7	7	3.3	4	57.1	0	0.0	3	42.9	0	0.0
40–49	271	28.6	160	59.0	62	22.9	26	9.6	23	8.5	28	13.1	14	50.0	4	14.3	6	21.4	4	14.3
50–59	379	40.1	183	48.3	116	30.6	56	14.8	24	6.3	79	36.9	13	16.5	16	20.3	23	29.1	27	34.2
60–69	190	20.1	83	43.7	56	29.5	31	16.3	20	10.5	82	38.3	9	11.0	23	28.0	26	31.7	24	29.3
70–79	41	4.3	17	41.5	12	29.3	6	14.6	6	14.6	18	8.4	4	22.2	4	22.2	4	22.2	6	33.4

Group I—Systolic up to 140
Diastolic up to 90

Group II—Systolic 141–160
Diastolic 91–100

Group III—Systolic 161–200
Diastolic 101–110

Group IV—Systolic over 200
Diastolic over 110

centage of cases of coronary occlusion, as well as some progressive increase in the number of cases belonging to the higher blood pressure groups. Beyond 59 years of age the incidence of coronary occlusion diminishes, whereas the percentage increase in the number of cases with rising blood pressure progresses. In all age groups in males, however, the incidence of the lower blood pressure levels among all cases of coronary occlusion is far greater than the incidence of the higher levels.

In females there is a progressive rise of the incidence of coronary occlusion up to and including 69 years of age, as well as a much greater progressive increase in the number of cases belonging to the higher blood pressure groups. Beyond 69 years of age there is a marked drop in the incidence of coronary occlusion and the percentage of cases in the lower blood pressure group appears to be relatively greater than in the earlier ages. Up to the age of 50 years, however, even in females there is a

relatively greater percentage of cases belonging to the lower blood pressure groups, while beyond that age the predominance of cases was in the higher blood pressure groups, the rise being progressive.

Age at Death: Table 2 summarizes the proportion of cases that died in the various age and blood pressure groups. Inasmuch as the number of cases was small, the male and female components were combined. This of course modifies the incidence of hypertension in the various groups.

About 15% of the deaths were caused by conditions other than cardiac disease, such as cerebral accidents, cancer, operations, and so on. Most of the deaths due to cerebral vascular hemorrhage or other accidents, comprising about 5% of the entire series, belonged to the Group IV hypertensives. About 20% of additional deaths were due to left heart failure, and most of these were in the blood pressure Groups III and IV.

TABLE 2

Average Age at Death, in Decades, in Normotensive and Hypertensive Males and Females Who Have Had at Least One Attack of Coronary Occlusion

Ages	Total Cases		Group I		Group II		Group III		Group IV	
	No.	%	No.	%	No.	%	No.	%	No.	%
All ages	363	100.0	124	34.5	95	26.2	74	20.4	70	19.2
20–29	1	0.3	1	100.0	0	0.0	0	0.0	0	0.0
30–39	5	1.3	4	80.0	0	0.0	0	0.0	1	20.0
40–49	39	10.7	15	38.5	11	28.2	7	17.9	6	15.4
50–59	126	34.7	47	37.3	34	26.9	27	21.5	18	14.3
60–69	127	35.0	37	29.1	33	25.9	25	19.7	32	25.2
70–79	65	18.0	20	30.8	17	26.1	15	23.0	13	20.0

Group I—Systolic up to 140, Diastolic up to 90

Group II—Systolic 141–160, Diastolic 91–100

Group III—Systolic 161–200, Diastolic 101–110

Group IV—Systolic over 200, Diastolic over 110

It will be observed that in the group of 20 and 29 years of age there was one death, a 25 year old male who died two weeks after the onset of coronary occlusion. He was normotensive. Between 30 and 39 years there were five deaths, four from the normotensive blood pressure Group I and one from Group IV. The latter was a female who died of uremia. Between 40 and 59 years of age about 38% of deaths were in Group I and about 28% more in Group II, with a total 66% of cases occurring in normal or mildly hypertensive cases. Only about 34% were in the severe hypertensives. After 60 years a somewhat greater percentage of cases that died belonged to the severe grades of hypertension, but the other two groups still predominated.

It will thus be seen that no deaths due to coronary disease occurred in the hypertensive group before 40 years of age. After that age there is an increasing percentage of hypertension cases dying following coronary occlusion. This increase appears to correspond to the increasing percentage of cases that normally develop a rising pressure in advancing age.

Length of Survival Following the First Attack of Coronary Occlusion: Table 3 summarizes the number and percentage of cases still living after one year, five years and 10 years, respectively, following the first attack of coronary occlusion among the males and females in the various blood pressure groups. It will be observed that a somewhat greater percentage of males than females was alive in the respective periods. This, however, probably reflects the far greater number of males in the entire series, so that the element of chance comes into play.

A larger percentage of cases in the various years survived in the blood pressure Groups I and II among males and Groups III and IV among females. This might perhaps suggest that the higher blood pressure in females is beneficial and is conducive to a longer period of survival from coronary occlusion. However, the discrepancy is more likely due to the

TABLE 3
Survival Following First Attack of Coronary Occlusion

Alive After	Total Cases		Group I		Group II		Group III		Group IV	
	No.	%	No.	%	No.	%	No.	%	No.	%
Males (946)										
1 yr.	760	80.4	383	50.4	214	28.1	101	13.3	62	8.2
5 yrs.	311	32.8	148	47.6	94	30.2	43	13.8	26	8.4
10 yrs.	70	7.4	33	32.8	24	34.3	9	12.8	4	5.9
Females (214)										
1 yr.	163	76.2	36	22.1	30	18.4	48	29.4	49	30.1
5 yrs.	51	23.3	8	15.7	13	25.5	18	35.3	12	23.5
10 yrs.	12	5.6	2	16.6	2	16.6	6	50.0	2	16.6

relatively greater percentage of hypertensives in females than in males. It may also be due partly to the relatively smaller number of females than males comprising this series, thus bringing the factor of chance into play.

DISCUSSION

It is seen from our findings in this series of 1,160 cases of coronary occlusion that the ratio of occurrence of this condition in males and females is about 4.4 : 1, while percentage frequency of hypertension in males is about one-half that in females. It is also observed that the incidence of both coronary occlusion and hypertension increases progressively with age in the males and in the females, but the proportional increase in coronary occlusion does not correspond to the increase in hypertension in both sexes in the various age groups. Also, in females a greater percentage of cases who had developed coronary occlusion in all age groups over 40 years had hypertension, while in males a greater percentage had normal blood pres-

sure, or a slight tendency to hypertension. Coronary occlusion appears earlier in life in males than in females, and reaches a fastigium earlier. Males also die earlier, although the number of cases having an average survival period of one year, five years and 10 years following coronary occlusion appears to be greater in males than in females. However, in males the number of cases with the longer survival is in the lower blood pressure groups, while in the females it is in the higher blood pressure groups.

These findings would tend to speak against causal relationship between hypertension and coronary occlusion. That the incidence of both conditions increases with advancing age is well established. If hypertension should be an important underlying cause of coronary occlusion, we would expect the increase of coronary occlusion to correspond closely to the increase in hypertension as age progresses. Furthermore, if there is causal relationship it is hard to understand why the incidence of hypertension is so much greater in the female group of coronary occlusion, at the same time that the incidence of coronary occlusion is so much greater in the males and in cases with low blood pressure levels.

The theory that there is something in hypertension of females which increases and of the males which decreases the tendency to coronary occlusion [5] appears to be unwarranted. In the first place, as was said before, coronary occlusion in females is far less frequent than in males in all ages, whereas the incidence of hypertension is greater. Second, although there is a relatively greater frequency of hypertension in coronary occlusion in females, such increase appears to be due to the relatively greater frequency of female hypertensives, as well as to the discrepancy in the number of cases in the two sexes, bringing the factor of chance into play. Third, for hypertension to be a factor in coronary occlusion we must assume that the blood pressure itself is an exciting factor in the causation of coronary occlusion. This would imply that certain anatomic changes are produced in the coronary vessels by the hypertension which increases their frequency to occlusion. It is difficult to see how this would occur in females and not in males. Furthermore, although unfortunately pathologic studies are meager, from available reports in the literature it appears that hypertension does not produce the characteristic background in the coronary vessels for occlusion. The vascular changes in hypertension occur mainly in the arterioles and in the capillaries throughout the body. Even these occur far less frequently in the coronary arteries than in those of other parts of the body.[21–25] In an autopsy study of 48 cases of malignant hypertension, Odel [24] found that the main changes in the coronary arterioles were confined to the media. They consisted of increase in the muscular elements. The intima showed only mild changes. There were only a few instances of partial occlusion of the lumen. He found complete occlusion of the major coronary vessels in only two cases. In occlusive arterial disease, on the other hand, the main changes consist of intimal degeneration.

Hypertensive heart disease is of course a definite disease entity, but its pathology and clinical manifestations are more or less distinctive. Harrison and Wood [26] stressed the essential differences in this form of heart disease from the ischemic form. The main coronary vessels in pure hypertensive heart disease are larger and of smooth bore, while in the ischemic form they are narrow and frequently occluded. Clinically, heart failure is the outstanding manifestation in the hypertensive heart, whereas the anginal syndrome is the outstanding feature in the ischemic heart, especially in the early phases. That both conditions frequently coexist is an established fact and is shown in our series. It is questionable, however, if atherogenesis of the coronary system is influenced to any extent by hypertension. That it may have some effect is a possibility, however.

We must add here that the term "ischemic heart," in contradistinction to the term "hypertensive heart," is perhaps inappropriate. In pure hypertensive heart disease more or less myocardial ischemia is also present. However, the ischemia in pure hypertensive heart disease is relative, caused by increase in the heart muscle mass in relation to the capillary blood supply and perhaps also to arteriolar changes. In myocardial ischemia due to coronary atherosclerosis the ischemia is caused by insufficient delivery of blood to the heart muscle, due predominantly to endarterial degenerative changes.

The question as to whether hypertension alters the prognosis in coronary occlusion can perhaps also be answered in the negative from our findings. From the superficial appearance of table 3 we would be inclined to feel that of the males the normotensives lived longer than the hypertensives, and that the reverse is true of the females. This again reflects the relatively greater percentage of females with hypertension and of males with coronary occlusion. The element of chance thus probably comes into play. This is further evidenced by the fact that in females both the incidence and the longevity of hypertensive cases who suffered coronary occlusions are greater, which would appear to be contradictory.

Our findings would explain the discrepancies in the incidence of hypertension in coronary occlusion reported by various authors mentioned in the early part of this paper. The incidence of hypertension would depend on the relative number of females and males in a given series, as well as on the relative ages of the patients comprising the given series.

Summary

A study was made of 1,160 cases of coronary occlusion to determine whether hypertension affects the incidence and prognosis of the disease. The series consisted of 946 males and 214 females. Of these, 797 were still alive and 363 were dead at the time this report was compiled.

The cases were divided into four blood pressure groups, as follows: Group I, systolic up to 140, diastolic up to 90; Group II, systolic 141–160,

diastolic 91–100; Group III, systolic 161–200, diastolic 101–110; and Group IV, systolic above 200, diastolic above 110. In the last group there were some cases with blood pressures as high as 300 systolic and 170 diastolic.

Each blood pressure group was subdivided into ages in decades when the first attack of coronary occlusion occurred in males and females; the average longevity following the first attack of coronary occlusion, and the length of survival of more than one year, five years and 10 years following the first attack of coronary occlusion.

The ratio of males to females who had coronary occlusion was 4.4 : 1, while percentage-wise, hypertension was about twice as frequent in females as in males.

It was found that, in males, coronary occlusion begins to appear earlier in life and its incidence progressively rises, reaching a fastigium between 50 and 59 years. The same is true of females but here the fastigium is reached between 60 and 69 years. The incidence of hypertension likewise increases with age, but such increase does not correspond strictly to the increase in coronary occlusion. Relatively more males than females in the over-all age groups who had the first attack of coronary occlusion belonged to the lower blood pressure groups. Up to 50 years of age, however, even females had a relative predominance of cases in the lower blood pressure groups.

Of the 363 patients who died, the few who died before 40 years of age were all in the normotensive group, except for one who died from uremia who was markedly hypertensive. After that age, there was a progressive increase in deaths following coronary occlusion with advancing age, but such increase did not correspond to the increase in blood pressure. A greater percentage of males than females lived more than one, five and 10 years following occlusion. However, a greater percentage of hypertensive than normotensive females survived these periods.

The figures do not appear to indicate that hypertension has any definite causal and prognostic relationship to coronary occlusion. The discrepancies in the figures are considered to be due to differences in the number of male and female patients in this series who had coronary occlusion and to the relatively greater percentage of female hypertensives.

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LATE CLINICAL CHANGES FOLLOWING THE INTERNAL DEPOSITION OF RADIOACTIVE MATERIALS *

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INTRODUCTION

THE increasing medical, military and industrial use of radioactive materials has made the knowledge of the late effects of internally deposited radio-elements of considerable importance. The principal sources of clinical material are individuals who were employed as luminous dial workers, individuals who received radium medically, and individuals who received Thorotrast in diagnostic radiology 10 to 40 years ago.

The information gained from the study of the late effects of internally deposited radioactive materials can be used in the following ways: (1) The clinical information will serve as a guide for the diagnosis, management and treatment of patients who may ingest or receive harmful amounts of radioactive materials. (2) The radiobiologic data obtained by new and refined technics can give a better understanding of the manner in which changes are produced by internally deposited radio-elements. (3) The information can be used to establish more accurately maximal permissible levels of body burden for these and other radio-elements in use today.

RADIUM

Radium was given intravenously and orally from about 1915 to 1939.[2, 25] The medical use of radium was based primarily on the belief that it relieved pain, activated enzymes and reduced blood pressure. Listed below are some of the most common conditions for which radium was given:

Hypertension	Neuritis	Infected wounds
Cardiovascular disease	Diabetes	Skin disorders
Arthritis	Mental disease	Anemias
Duodenal ulcers	Buerger's disease	Leukemia
Gout	Syphilis	Nephritis

Fifty patients who received radium for medical purposes and 28 luminous dial workers were recently evaluated.[6, 19] The mean age of the luminous dial workers at the time of employment was 20 years, and the mean age at the time the individuals received radium medically was 35 years. The

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The opinions and assertions contained herein are the private ones of the writer and are not to be construed as official, or reflecting the views of the Navy Department or the Naval Establishment at large.

radio-elements had been deposited in the body for about 25 years in both groups of patients.[17]

Deposition and Histopathology

"Radium stored in the body is analogous to lead in distribution, mode of excretion and relationship to calcium metabolism." [5] Radium was found in small areas of high focal concentration distributed irregularly throughout the skeleton. The areas of radium concentration in cancellous bone were usually about 5 to 15 microns in the greatest dimension, with a wide variation in size and shape. Only about 10 to 15% of the haversian systems had high concentrations of radium.[4, 13, 21]

Atypical osseous tissue was found in the trabecular spaces of cancellous bone, adjacent to the trabeculae. The remainder of the trabecular spaces were usually filled with acellular fibrous tissue.[12, 16] The central canals of the haversian systems had a marked variation in size from normal to where the entire haversian system was almost completely destroyed. Some of the central canals were occluded with a dark-staining material similar to the atypical osseous tissue. Macroscopic areas of destruction were present in compact bone, which were usually 1 to 2 mm. in width and 5 to 20 mm. in length.[6, 16, 21]

In combined autoradiographic, histopathologic and roentgenographic studies, the histopathologic changes were found as often in the absence as in the presence of radium concentrations.[16, 21] In view of these observations it is considered that radium does not always cause pathologic alterations from the direct effect of ionizing irradiation. Radium deposited in the skeleton may initiate a sequence of events that eventually produces pathologic changes. These changes are probably the end results of many augmenting factors such as trauma, damage to blood supply, decreased bone repair, hormonal balance, etc. It is reasonable to conclude, therefore, that when the destructive effects of radium and other deleterious factors become greater than the reparative processes of the skeleton, permanent alterations occur.[21]

Roentgenographic Findings

Small areas of increased density were found roentgenographically in cancellous bone as a result of atypical osseous tissue formation. Small areas of decreased density were found in compact bone as a result of the small, well defined areas of bone destruction.[6, 16]

The roentgenographic changes were divided into three groups.

Group I Areas of decreased density:

A. Longitudinal areas which occur in the long bones and give a "streaked" appearance. These areas are usually 1 to 2 mm. in width and 5 to 20 mm. in length.

B. Well differentiated areas which vary from 2 to 20 mm. in the greatest dimension and which may be oval, square or irregular in outline. They usually occur in the skull, long bones and bones of the feet.

Group II Areas of increased density, usually associated with varying degrees of decreased density and change in trabecular pattern.

These changes present a "mottled" or "moth-eaten" appearance, and they usually occur in the heads of the femora and humeri, and in the glenoid process.

Group III Changes in the normal configuration and areas of destruction.

The term "aseptic necrosis" has been used in referring to these changes. The heads of the femora, bones of the feet and mandible were most commonly involved.

If skeletal changes characteristic of radio-element deposition are present they can usually be detected by a roentgenographic examination of the most commonly involved bones, namely, fibulae, femoral heads and radii.

Symptomatology

Symptoms which can reasonably be attributed to radium deposition occur from changes in the skeleton. The increase in fragility of the skeleton may result in fractures and aseptic necrosis following minimal trauma. Symptoms which could reasonably be attributed to radio-element deposition in the 78 patients of the Chicago-Boston investigations began from one to 32 years following deposition. The average time for symptoms to occur was about 15 years. Symptoms attributable to radio-element deposition occurred sooner in the luminous dial workers reported by Martland in 1931. Some of these patients had 10 to 100 times as much radium as patients of the recent investigations.[24] The symptoms which could reasonably be attributed to radio-element deposition are listed below [6, 17] (table 1).

Table 1

Skeletal Symptoms Attributed to Radio-element Deposition

Involved Part	No. of Patients	Involved Part	No. of Patients
Mandible	15	Humeral head	
A. Sequestration		Aseptic necrosis	1
B. Non-union			
C. Partial loss		Radial head	
		Aseptic necrosis	1
Femoral head	10		
Aseptic necrosis		Tarsal scaphoid	1
		Aseptic necrosis	
Femur	5		
Fracture		Metatarsal	1
		March fracture	

TABLE 2

Malignancies Found in Boston–Chicago Investigations (78 patients, 1951)

Luminous Dial Workers		Radium Patients	
Type of Malignancy	Time from Deposition to Death (Years)	Type of Malignancy	Time from Deposition to Death (Years)
Carcinoma accessory nasal sinuses	34 yrs.	Osteogenic sarcoma (humerus)	23 yrs.
Carcinoma mucosa temporal bone	33 yrs.	Fibrosarcoma (femur)	17 yrs.
Carcinoma (paranasal sinuses)	19 yrs.	Osteogenic sarcoma (1st metacarpal)	29 yrs.
Giant cell tumor (mandible)	13 yrs.	Osteogenic sarcoma (tibia)	24 yrs. (?)
Osteogenic sarcoma (elbow)	living	Fibrosarcoma (tarsal-scaphoid)	22 yrs.
Osteogenic sarcoma (ischium)	27 yrs.		
Osteogenic sarcoma (femur)	32 yrs.		
Osteogenic sarcoma (tibia)	27 yrs.		

TUMOR FORMATION

Most of the patients who eventually develop malignancies follow a similar course. There is a latent period followed by symptoms which usually develop as a result in changes in weight-bearing bones and bones which are subjected to repeated trauma. The malignancies which developed later did not occur at the sites of the initial symptoms. Death usually occurred in about one to four years after symptoms developed at the site of tumor origin, and about nine years after the initial symptoms occurred. The period from the time of radio-element deposition until the initial symptoms was about 15 years for the patients recently evaluated. The latent period for Martland's cases reported in 1931 was about eight years. These patients, however, had greater amounts of radioactive materials present in their bodies.[17]

The site of origin of the malignancies that developed in the Boston and Chicago investigations and the length of time from the deposition of the radio-elements until death are given in table 2.[6, 17, 19]

HEMATOLOGIC FINDINGS

The marked pancytopenia that developed in some of Martland's cases did not occur in the recent investigations.[6, 16, 23, 24, 27] Minor changes in the erythrocytes were more frequent in patients having greater amounts of retained radium. There were usually a slight anisocytosis, poikilocytosis and mild hypochromia. However, the erythrocytes of some of the patients who had the greatest amount of radium were normal. The erythrocyte

sedimentation rate in 34 of 39 patients was elevated above 20 mm. in one hour.[16, 19]

Laboratory Data

The serum calcium, phosphorus and alkaline phosphatase values are usually within normal limits. The serum calcium and phosphorus may become depressed terminally. The alkaline phosphatase may be elevated or depressed.[6, 17]

Thorium

Thorium dioxide (Thorotrast) began to be used in diagnostic radiology in this country in about 1930. It was used as a radiopaque medium for visualization of the liver and spleen, cerebral arteriography, ventriculography, etc.[26, 28, 32, 34, 35] Thorotrast has been used less and less in recent years because of the formation of dense fibrotic reactions following the extravasation into the tissue at the sites of injection and because of the potential carcinogenic effects from the radioactivity.[5, 7, 26, 29, 32]

Some of the conditions for which Thorotrast was used are listed below:

A. Visualization of Liver and Spleen
   1. Amebic abscesses
   2. Cirrhosis of liver
   3. Metastases to liver

B. Cerebral Arteriography
   1. Anomalies
   2. Aneurysms
   3. Hemangiomas

C. Ventriculography
D. Encephalography
E. Disorders of Genitourinary Tract
F. Mammography
G. Arteriography of Extremities
   1. Arteriosclerosis
   2. Hypertension
   3. Buerger's disease
   4. Aneurysms

Table 3 gives a list of follow-up studies made on patients who had previously been given Thorotrast.

Deposition and Histopathology

Thorotrast contains 25% thorium dioxide by volume, and about the same amount of protective colloid, a dextran preparation.[22] Thorium is phagocytized by the reticuloendothelial system and retained indefinitely.[15, 18, 32]

TABLE 3

Follow-Up Studies (Thorotrast)

Type of Investigation	Number of Patients	Results	Investigator	Year
Three yr. follow-up	175	No deleterious effects found	Rigler et al.[28]	1935
Ten yr. follow-up	286	No deleterious effects found	Yater and Coe[34]	1942
Patients who had Thorotrast in soft tissue of neck	7	Induration and symptoms from local reaction	Amory and Bunch[3]	1948
Fifteen yr. follow-up	235	4 anemias, 1 leukemia Minor hematological changes 5 splenectomies for splenic colic	Johansen et al.[15]	1949
Survey of 132 radiologists	4235	Two unpublished malignancies	Thomas et al.[32]	1951
Twenty yr. follow-up	17	1 leukemia 4 abnormal liver function tests 4 patients, induration at site of injection Minor skeletal roentgenographic and hematologic changes	Looney and Colodzin[18]	1952

Larger and larger aggregates of Thorotrast collect with increasing time following administration. The primary sites of deposition are the liver, spleen and bone marrow, with lesser degrees in the lungs and adrenals. Minute amounts of thorium are found throughout the body. Histopathologic changes in the liver, spleen, lymph nodes, adrenals, bone marrow and skeleton [15, 16, 22, 26, 30, 32, 33, 36] have been reported following Thorotrast administration. In general, there is comparatively little clinical reaction and destruction to the presence of Thorotrast.[15, 16, 26, 28, 33, 34, 35] Exceptions to this, however, were in the spleen and at those sites of the injection where there was extravasation of Thorotrast into the soft tissue. The major part of the architecture of the spleen may be replaced by fibrous connective tissue, and marked induration and fibrous connective tissue proliferation may be present following extravasation.

ROENTGENOGRAPHIC CHANGES

In patients in whom extravasation of Thorotrast has occurred, areas of increased density are found roentgenographically. The liver and spleen have varying degrees of increased density, depending upon the amount injected. Minor skeletal roentgenographic changes have been found in over 50% of the Naval Medical Center Series (17 patients). These changes consisted in thickness of the shafts and trabecular markings, and irregularity of the endosteal surfaces of the long bones.[18] Further work is in prog-

ress to determine if there is a relationship between Thorotrast administration and the roentgenographic changes.

Symptomatology

The only symptoms attributable to Thorotrast administration in the Naval Medical Center Study were from induration as a result of extravasation.[18] Five patients of the Denmark study had splenectomies, with reported improvement of a vague type of pain in the abdomen and around the left costal region.[15]

Hematologic Changes

Minor changes in the hemoglobin, erythrocytes, leukocytes and lymphocyte counts were found in both the Denmark and the Naval Medical Center investigations.[15, 18] Only five anemias have been reported as having developed in individuals following the use of Thorotrast.[7, 15, 30, 31]

Laboratory Data

All of the patients of the Naval Medical Center Series had complete liver function tests, and four of the 17 had one or more abnormal liver function tests. At present, we are unable to attribute these abnormal functions to the presence of Thorotrast. The possibility of Thorotrast's being a contributing factor cannot be dismissed. Other laboratory tests were noncontributory.[18]

Malignancies

Primary malignancies of the liver have been found in five patients following the use of Thorotrast.[9, 15, 22, 32] Three unpublished leukemias have been found.[11, 15, 20] One bilateral alveolar lung cancer has been reported following Thorotrast administration.[1] Malignancies at the sites of injection have occurred in five patients, two following injection of Thorotrast into the lacrymal ducts, one following the injection of the maxillary sinus, one following the injection of the ducts of the breast, and one following retrograde pyelogram.[10, 14, 15, 29, 37]

Summary and Conclusions

A. Radium

1. Almost all of the radium is eliminated when taken into the body.
2. The retained radium is deposited irregularly in the skeleton in small areas of high radium concentration.
3. Roentgenographic changes characteristic of radio-element deposition develop many years after administration. Areas of decreased density occur in compact bone as a result of bone destruction. Areas of increased density occur in cancellous bone as a result of atypical osseous

tissue formation. Areas of decreased density on skeletal roentgenographic examination may be the first clinical evidence of malignancy.
4. Increased fragility of skeleton occurs as a result of radium deposition and fractures and aseptic necrosis occur with increased frequency.
5. Minor hematologic changes may be present, and, infrequently, aplastic anemias may develop.
6. Skeletal malignancies may develop as long as 10 to 30 years after radio-element deposition.

B. THORIUM

1. Almost all of the administered thorium from Thorotrast is indefinitely retained.
2. Its primary sites of deposition are the liver, spleen and bone marrow, with lesser concentrations in the lungs, adrenals, etc.
3. Histopathologic changes in the liver, spleen, lymph nodes, adrenals, bone marrow and skeleton have been reported following Thorotrast administration.
4. In general, there is comparatively little reaction clinically to the presence of Thorotrast and the resulting irradiation. Exceptions to this, however, were in the spleen and at those sites of injection where there was extravasation of Thorotrast into the soft tissues.
5. The presence of Thorotrast can be demonstrated roentgenographically in the liver, spleen and sites of extravasation in the neck and arms.
6. Slight thickening of the shafts and trabecular markings with irregularity of the endosteum have been demonstrated roentgenographically.
7. Symptoms may develop from the marked contraction and induration at the sites of injection.
8. Minor hematologic changes have been found in patients who received Thorotrast, and a small number of anemias have been reported. Some patients have abnormal liver function tests. The interpretation is difficult because of the underlying disease for which Thorotrast was given.
9. No definite conclusions can be drawn concerning the possible relation between Thorotrast and the small number of malignancies and leukemias thus far reported.

C. IMPORTANCE OF CONTINUING THESE INVESTIGATIONS

1. In general, relatively little is known about the late effects of internally deposited radioactive materials in man.
2. Almost nothing is known about the late effects in man of plutonium and other radio-elements which are in military, medical and industrial use today.
3. Use of radium in the luminous dial industry and in medicine began about 1915. Use of thorium in diagnostic radiology began about

1930. Hundreds of these people who have had radioactive materials present in their bodies for long periods of time are available.

4. Recognition of the clinical findings which the practicing physician may utilize in making a diagnosis of previous radio-element deposition offers the best means for locating these individuals.
5. It is only through location and continued reëvaluation of large numbers of these individuals that we may more accurately determine what the late effects of internally deposited radioactive materials are and thus more adequately protect the increasing numbers of the population who may be exposed.

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THE SURGICAL TREATMENT OF AORTIC INSUFFICIENCY *

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INTRODUCTION

REGARDLESS of the etiology, aortic insufficiency produces the dynamic effects of an aorticoventricular fistula which are expressed only during diastole. The abnormal communication between these two adjacent and high pressure segments of the circulatory system results in a reflux of blood into the ventricular chamber which may amount to as much as one-half or more of the systolic output. The magnitude of the incompetence determines the amount of regurgitation and the subsequent physiologic alterations in the circulation. The increased volume of blood in the left ventricular cavity during diastole produces an initial dilatation of that chamber which is followed by hypertrophy, and in significant instances the subsequent enlargement may transcend that produced by any other type of cardiac disorder (figure 1).

Classically, the prognosis in rheumatic aortic insufficiency has been considered favorable, with patients able to maintain uninterrupted compensation for years if not for a normal length of life. This experience unquestionably stems from grouping patients with all degrees of aortic insufficiency in a single classification. It is the contention of the authors, on the basis of present experiences, that the lesion is often not benign, and that the severity of the clinical picture in a considerable proportion of patients justifies the current and any continuing search for the surgical correction of the defect. During the developmental phase of the present surgical technic for aortic insufficiency, 12 patients ranging in age from 22 to 43 years were followed for six months. By the time the operative procedure was considered sufficiently developed for application, eight of them had died of massive myocardial infarction, the sudden development of ventricular fibrillation, or of congestive heart failure. Two were too ill to warrant surgery. Certainly a further clinical evaluation of aortic insufficiency is justified on the basis of its physiologic significance, the ordinary complications which develop in its natural history, and its effect in the presence of associated lesions.

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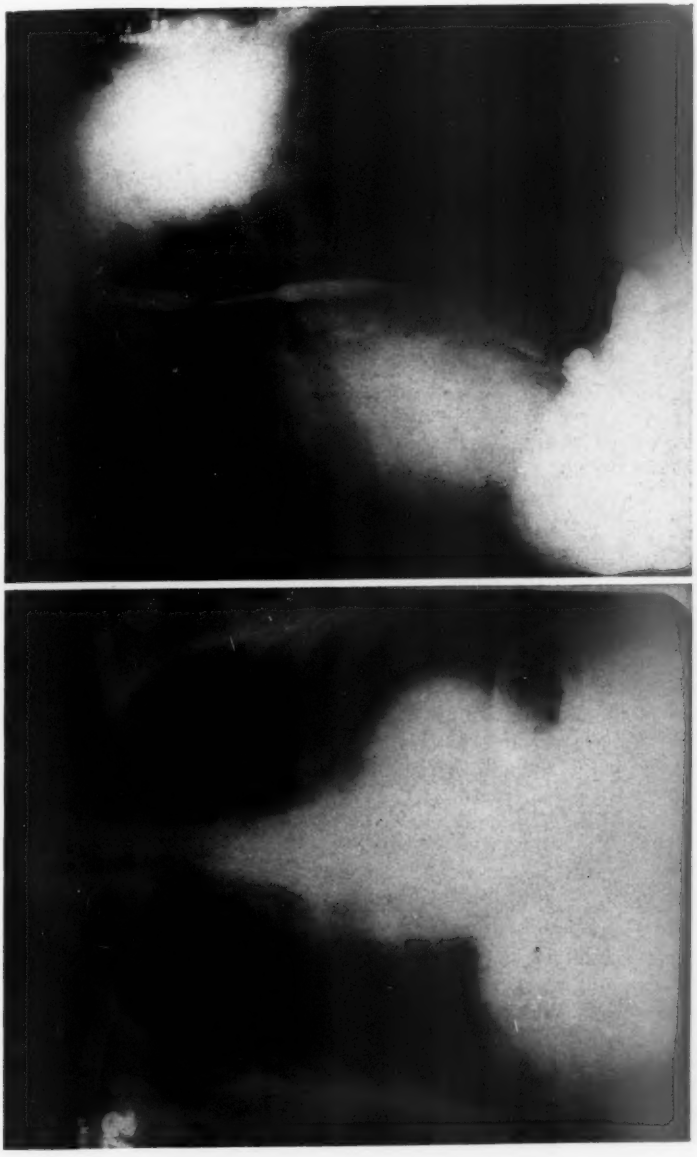


FIG. 1. Roentgenograms showing typical bootlike enlargement of the left ventricle in aortic insufficiency. Note encroachment of left ventricle toward the vertebral column in oblique view.

Etiology

Aortic insufficiency is most commonly caused by rheumatic activity or syphilis. Occasionally it may result from congenital deformity of the valve cusps, from an accidental wound, direct surgical trauma, indirect trauma, or bacterial endocarditis. It is associated with hypertensive and arteriosclerotic vascular disease in a relatively small number of patients.

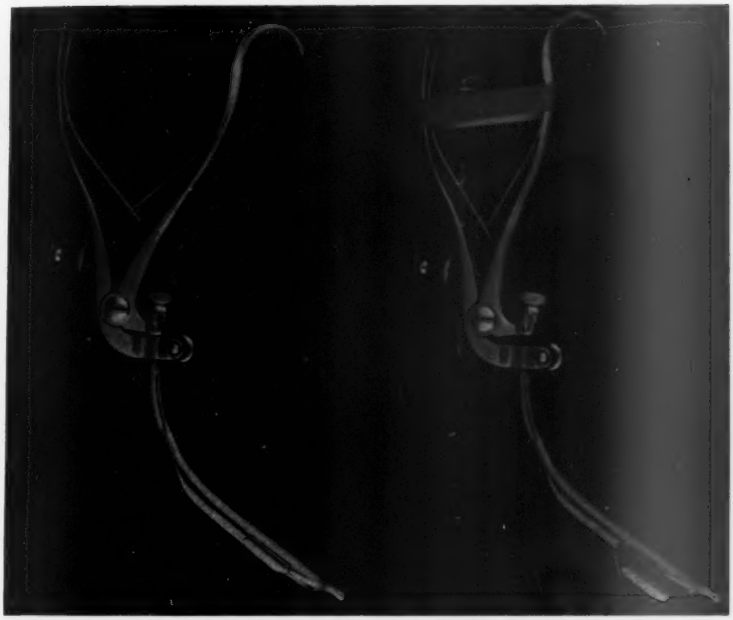
Congenital aortic insufficiency may be related to a perforation or an abnormal anatomic placement of the cusps, or, in other instances, to a bicuspid valve which results in an associated significant stenosis. At the moment we are not prepared to offer any technical approach applicable to these problems.

Trauma sufficiently severe to produce significant aortic insufficiency is rarely compatible with survival, and therefore does not often enter into present considerations. The lesion can be produced in the blind instrumental transventricular approach to aortic stenosis [1, 2, 3] unless the technic is safeguarded by a limited opening of the dilating blades. The more recently developed [4, 5] trans-aortic approach to the stenotic valve, which is based on the use of an instrument worn on the operator's left index finger, appears to have overcome this hazard because of the accuracy of digital guidance of the extent and direction (figure 2A and B) of commissural separation.

Subacute bacterial endocarditis develops only upon a valve previously deformed by congenital or acquired disease, and the resulting insufficiency must therefore be considered in the light of the basic etiologic factor.

Luetic aortic insufficiency, unlike rheumatic, classically results from a widening of the commissures, a shortening of the cusps, and a generalized dilatation of the annulus fibrosis due to destruction of its collagenous elements. Of these anatomic changes the most characteristic is the widening of the commissures, thought by Saphir and Scott [6] to be related to a fibrous adherence between the lateral portions of the cusps and the intima of the adjacent sinuses of Valsalva. This process in its progression may cause the coronary ostia eventually to empty into cystlike cavities with minute orifices. Although the cusps are never attacked directly, the distortion may be so effective as eventually to produce a widely dilated ring with an irregular, incompetent edge of valve tissue about its margin.

Rheumatic activity produces much of its effect through pathologic changes beginning at the aortic valve ring and then progressing centrally to create thickened and deformed cusps associated with fusion of the commissures. It is probable that the organization of fibrinous deposits upon the surfaces of the cusps produces the same type of valvular thickening and commissural fusion characteristic of the pathogenesis of rheumatic mitral stenosis. Both Rokitansky [7] and Magarey [8] clearly have demonstrated these developments in the mitral valve. This organized exudative process produces elements of stenosis even as it creates the anatomic backdrop for



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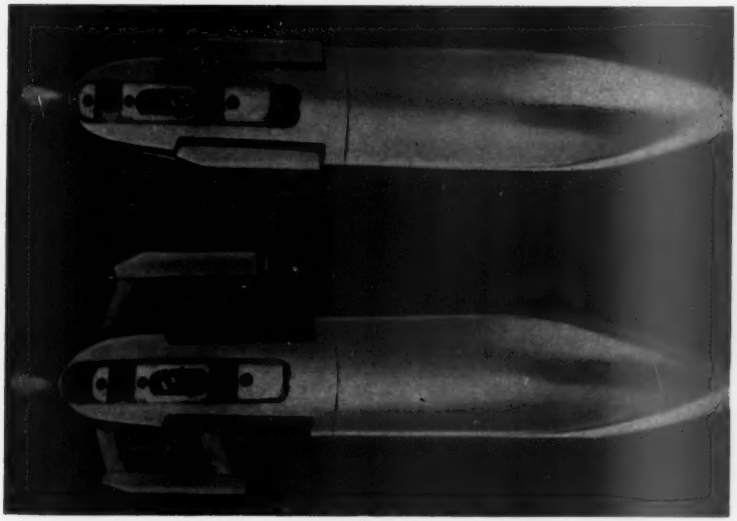


B

FIG. 2. A. Retrograde aortic dilator, side view. B. Retrograde aortic dilator, under view.

FIG. 3. A. Aortic valve, seen from above, early rheumatic valvulitis. B. Asymmetric stenosis with bicuspid transformation. C. Symmetrically stenotic aortic valve. In any of these conditions, there may be some coexisting aortic incompetence. (Larzelere, courtesy Journal of Thoracic Surgery.)

insufficiency. The predominant effect rests with the extent of the opposing changes, although an equal degree of stenosis and insufficiency is entirely possible. Where stenosis coexists the aortic orifice is reduced to a small triangular opening which may be centrally or eccentrically located and symmetric or asymmetric in contour. When the anterior commissure is completely obliterated the valve becomes bicuspid anatomically and functionally. The insufficiency develops from the associated shrinkage of the cusps, which renders coaptation impossible (figures 3A, B, C).

However, highly significant aortic insufficiency reflected by all the classic clinical findings has been observed in patients in whom the aortic valve cusps appeared entirely normal at autopsy. The explanation for this apparent paradox rests with the resilience of the annulus fibrosus. When this has

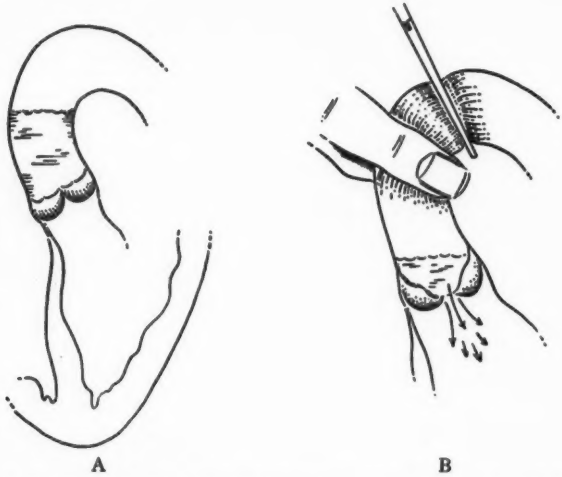


FIG. 4. A. In weakening of the aortic annulus, the ascending aorta may hold water in the autopsy room. B. Clamping the arch and squeezing the ascending aorta result in regurgitation of the contents into the left ventricle. This illustrates the condition found in life with normal levels of pressure.

been compromised by the pathologic changes incidental to rheumatic activity the elastic recoil of the aorta at the valve level becomes reduced and coaptation of the cusps consequently is imperfect or impossible. If coaptation does momentarily occur, the annulus can not successfully oppose the intra-aortic diastolic pressure which distends the aortic wall in this region, thereby producing valvular incompetence. When the valve is examined in the living patient through the trans-aortic approach in such instances the leaflets are flexible and the commissures are not fused. In the autopsy room the ascending aorta will support a column of water. However, clamping of the arch and squeezing of the ascending aorta will result in visible dilatation of the aortic root, and leakage into the ventricle (figures 4A, B).

During life the aortic orifice during systole is normal, and the only demonstrable abnormality is a narrow gap between the free margins of the leaflets during diastole, which often can be obliterated during trans-aortic surgery by holding the fingertip in the residual central aperture. This maneuver effectively reduces the regurgitant stream, since the diastolic thrill previously palpable at a point over the left ventricle or the root of the aorta disappears or dramatically diminishes. Withdrawal of the obstructing finger results in a return of the thrill. There is every reason to believe that abnormalities of the cusps and the loss of annular tensile strength may coexist, a situation which is well understood when it occurs in the mitral valve.

Clinical Manifestations

1. *Symptoms:* In patients with minor involvement there may be no symptomatic indication of the valve defect. Dynamic lesions, however, are accompanied by characteristic subjective and objective findings related to the cardiac status or associated complications. *Fatigability* is a universal complaint and frequently results in self-imposed restrictions through which the patient avoids more ominous symptoms. *Dyspnea* of varying intensity is present in the majority of patients and, contrary to present concepts, may exist for a considerable period unassociated with other manifestations of heart failure. *Syncope* and *vertigo* occur in approximately one fourth of the patients, and are probably related to cerebral vascular insufficiency. The attacks of unconsciousness usually occur at long intervals and are entirely unrelated to effort or position. Vertigo characteristically occurs with sharp changes in position, and is responsible for considerable and continuing incapacity.

Angina pectoris occurs in over half of the patients with combined rheumatic aortic stenosis and insufficiency. It is less common but equally incapacitating when insufficiency is an independent lesion. Although superimposed coronary arteriosclerosis may produce angina pectoris in the older age groups, this symptom is generally attributed to a disproportion between coronary blood flow and the demands of the greatly hypertrophied heart muscle. In luetic aortic insufficiency the cardiac pain can arise from the co-

existing stenosis of the coronary ostia. Paroxysmal dyspnea with left ventricular insufficiency is frequently observed.

Peripheral edema occurs in a third of the patients, even in the absence of associated valve lesions.

Embolic accidents are unusual except in the presence of complicating mitral disease.

Patients are frequently disturbed by the forceful apical thrust of the heart against the precordium, a symptom which is particularly annoying when lying on the left side. The pulsations of the carotid and brachial vessels are dramatic visual evidence of the peripheral changes in the vascular dynamics.

2. *Objective Findings:* The characteristic auscultatory finding is a high-pitched early blowing diastolic murmur which immediately follows the second aortic sound. The latter is usually diminished or absent. The murmur is usually heard best along the left sternal border in the third interspace or less frequently in the second right interspace. Frequently it is transmitted downward and laterally and may be well heard at the xiphoid process or at the apex of the heart. At times this murmur can not be overlooked in the most casual examination, but where involvement is more limited it may be recognized with great difficulty and only with the patient upright and leaning forward.

A systolic murmur heard best over the second right interspace frequently accompanies the diastolic murmur even in the absence of significant stenosis. An apical systolic murmur may also be present due to a relative mitral insufficiency which may follow dilatation of the left ventricular chamber.

Normal sinus rhythm is the predominant rhythm and actually was the only mechanism observed by the authors when mitral valve disease was not associated.

The main peripheral sign of dynamic aortic insufficiency is the low diastolic blood pressure, which generally is accompanied by an elevated systolic level. The resultant pulse pressure generally exceeds 60 mm. of Hg and frequently has been observed as high as 200 mm. Associated peripheral signs include the water-hammer pulse, capillary pulsations, and a disproportionate femoral systolic hypertension.

The roentgenologic examination of the heart in advanced lesions reveals a downward and lateral enlargement of the left ventricle in the postero-anterior view with a rounding of the apical shadow. In the left anterior oblique the enlarged chamber is visualized encroaching upon the shadow of the spine (figure 1). The aorta may be dilated, and on fluoroscopic examination the increased vigor of the ventricular contraction and aortic dilatation results in a characteristic rocking motion of the cardiovascular shadow. Other x-ray abnormalities depend upon the state of compensation or the presence of associated lesions.

In significant aortic insufficiency the electrocardiographic pattern is typical of left ventricular hypertrophy and "strain."

There is a typical ballistocardiographic pattern in aortic insufficiency (figure 5).

Brachial artery tracings reveal a sharp ascent of the initial limb associated with a downward displacement of the dicrotic notch and a broadening of the base of the descending limb of the curve (figures 12A, 14A).

The clinical manifestations permit a diagnosis without difficulty. A significant or dynamic involvement is identified by the presence of the peripheral vascular changes, notably the wide pulse pressure, and the abnormal brachial artery pressure tracing.

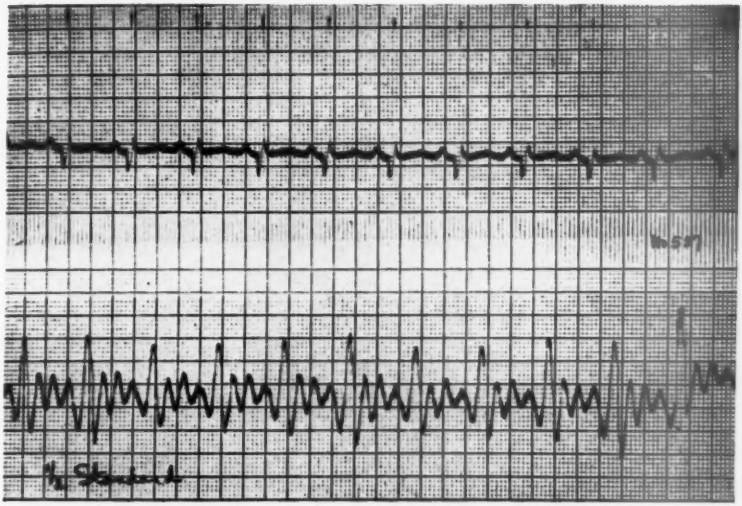


FIG. 5. Typical ballistocardiographic tracing in aortic insufficiency.

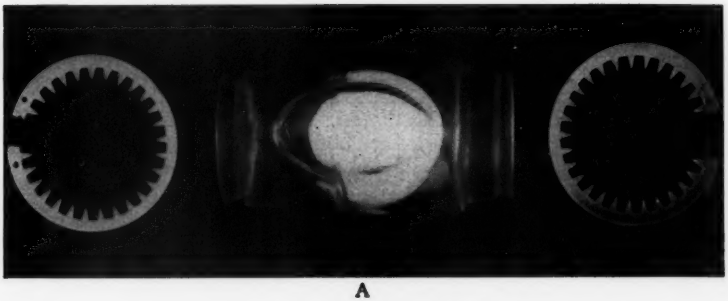
The clinical pattern of aortic insufficiency most commonly is terminated by the occurrence of congestive heart failure and full disability, or by sudden death attributed to ventricular fibrillation, or massive myocardial infarction which develops from the disproportional coronary blood flow.

SURGICAL EFFORTS AND CONCEPTS

Smithy [9] was the first to report the experimental creation of aortic insufficiency. Hufnagel [10, 11] has designed a prosthetic ball-valve of methyl methacrylate which is well tolerated in the continuity of the descending aorta, and abolishes the dynamic circulatory effects of insufficiency beyond the point of placement (figures 6A and B). Obviously, there can be no improvement proximal to the prosthetic. However, since blood which has passed the ball-valve cannot regurgitate into the left ventricle, the over-all efficiency of the circulation is improved. Unfortunately, for technical reasons this valve

can not be placed proximal to either the coronary ostia or the innominate artery. In Hufnagel's hands application of the prosthetic has resulted in clinical improvement, and the operative mortality has been acceptable.

On April 18, 1952, at the Annual Scientific Meeting of the American Heart Association, the authors presented a paper based on 15 early attempts to correct aortic insufficiency by the placement of a pedunculated ball or a hammock of pericardial tissue within the aortic lumen just above the level of the valve. It was believed that the free movement of these grafts pro-



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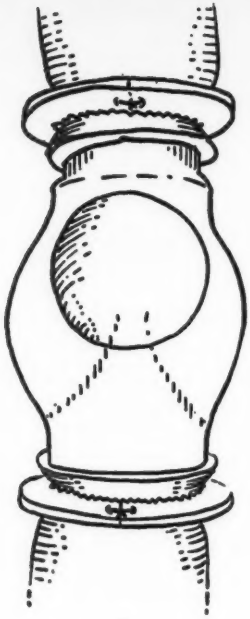


B

FIG. 6. A. Hufnagel valve. B. Hufnagel valve in place in aortic continuity.

duced a considerable tamponade of the valve opening. This concept was confirmed by the resulting elevations in diastolic blood pressures. Unfortunately, the manuscript and the details of the technic were never published. The passage of time and subsequent experience established three weaknesses in this early technic. First, the inability to palpate the valve made it difficult to place the pericardial tissue accurately above the regurgitant orifice. Second, the grafts swelled initially and then became fibrotic and eventually retracted from their tamponading position. Finally, the technic could not cope with the type of valvular dysfunction which results from a dilatation of the annulus.

FIG. 7. Cross section of heart at the level of the aortic valve. Note the deep location of the aortic valve and the course a constricting band would be required to take.

The development of the transaortic approach [4, 5] for the relief of aortic stenosis has permitted direct digital examination of the valve structures. Applied to the treatment of aortic insufficiency, this method allows digital guidance of the passage and placement of prosthetic materials within the aortic lumen, and establishes the degree of narrowing or constriction of the aortic annulus which may be created to insure proper valve function.

This early interest in the subject and an increasing understanding of the problems encountered as a result of our experimental and clinical efforts to alter the course of aortic valvular disease have led to two entirely different surgical approaches to the relief of aortic insufficiency. In one type, a soft belt or sash of nylon fabric is applied about the weakened and dilated aortic

annulus to constrict it sufficiently to bring about diastolic apposition of the free margins of the valve cusps. This method was worked out extensively in animals.[12] In patients with coexistent aortic stenosis this lesion is relieved first, if digital examination indicates it to be necessary, by performing a trans-aortic commissurotomy. Then, unless full competence of the valve leaflets has been restored by this means, a prosthetic flap or hammock valve is immediately placed in such a way as to block the portion of the aortic passageway which remains open during diastole.

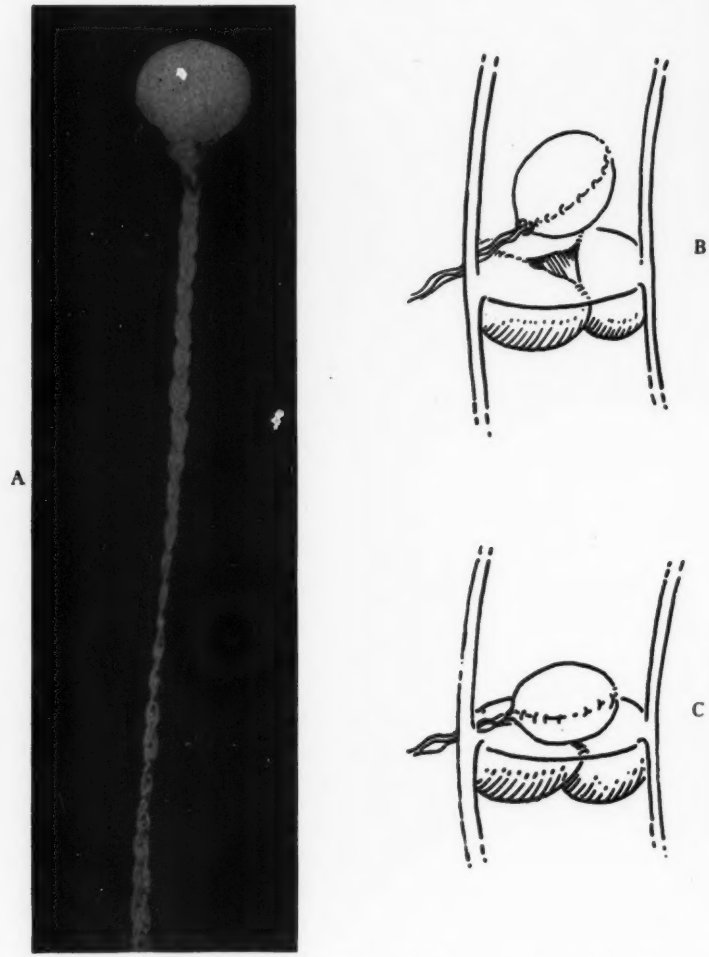
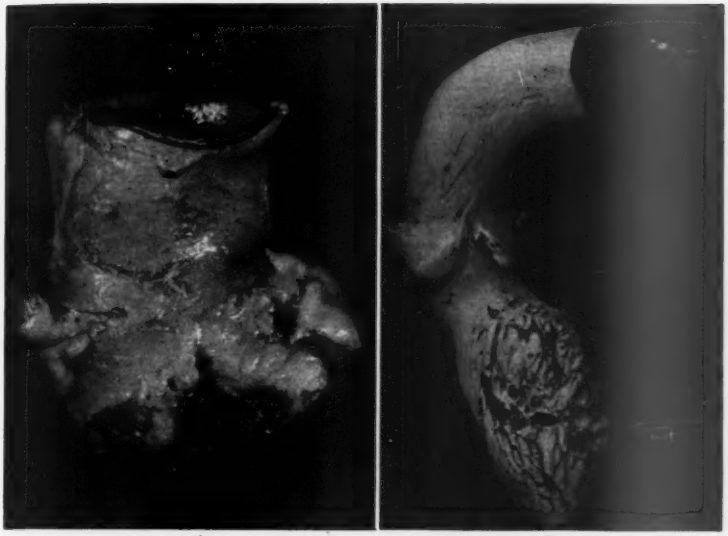


FIG. 8. A. Original "polliwog" valve. B. Placed polliwog during systole. C. Placed polliwog during diastole.



A B

FIG. 9. A. Anatomic structure of first portion of the aorta—photograph of autopsy specimen. B. Latex cast of aorta, showing narrowing above sinuses of Valsalva. Note ostia of coronary arteries.

It is understood that in mixed cases presenting features of both processes, both therapeutic methods must be applied simultaneously.

Tentative and Experimental Attempts at Correction of Aortic Insufficiency: Our first attempts to narrow the aortic annulus were based upon the known property of certain cellophane impurities to stimulate a constricting fibrosis when applied into the sheaths of blood vessels or when wrapped about them. However, the aortic ring lies so deep within the heart substance that such application proved too difficult for practical accomplishment.

An attempt to encircle superficially the first portion of the aortic root with a constricting band failed because of the conical shape of the aortico-cardiac junction. When a sash of nylon fabric is tied tightly about this region it tends to migrate upward and encircle the narrower aorta. If the sash has been placed beneath the first portions of the coronary arteries, its upward migration will pull them upward in crooklike fashion and obliterate their flow.

As a result of these ineffectual attempts the regional anatomy of these structures was further investigated. As is illustrated in the accompanying photograph and diagram (figure 7), a constricting band placed in such a way as to encircle the beginning of the aorta in the vicinity of the annulus must traverse both atrial chambers, penetrating the intervening atrial septum. Then it must pass deeply on the right through the left ventricular myocardium, dipping well beneath the right coronary artery. On the left

it must dip beneath the left coronary artery and then traverse the region of aortico-pulmonary arterial apposition. Both ends of such a sash can be brought into contact anteriorly between the right ventricular outflow tract and the root of the aorta (figure 23A). Tying of this band will then create the desired effect of annular constriction. This technic was worked out on experimental animals for nearly two years before making the first human operative attempt.[12]

A method of application of a prosthetic valve mechanism at the level of the natural orifice was equally difficult to develop.

At first, nylon fabric was rolled up into a small ball, perhaps 1 cm. in diameter, leaving an attached tail to the fabric. The resulting structure

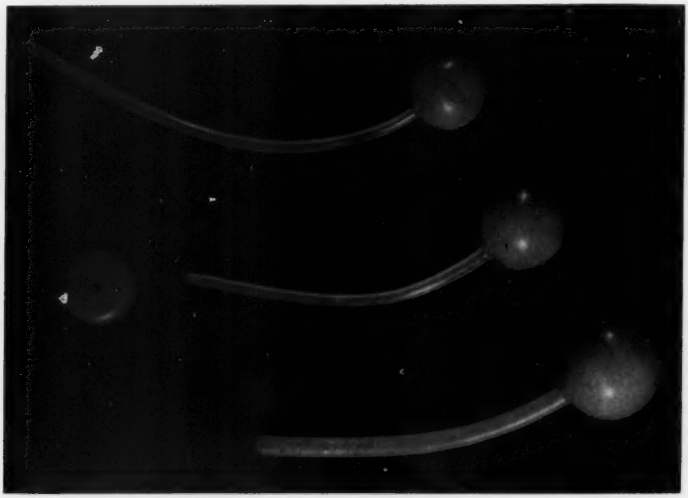
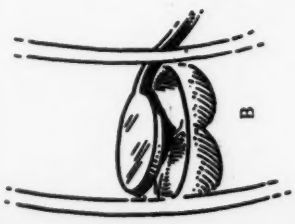
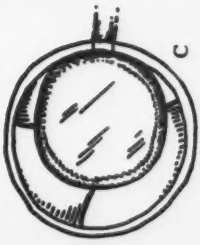


FIG. 10. "Polliwogs" of silicone rubber.

closely resembled a polliwog or tadpole. Once the technic of palpating the aortic valve orifice by the trans-aortic approach was perfected, it was possible to place such a prosthesis by guiding a threaded curved probe along the finger and through the aortic wall in the region of the anterior aortic commissure. Having grasped the thread and removed the probe, it was simple enough to draw the tail of the "polliwog" through this opening by attaching it to the internal end of the thread (figures 8A, B, C).

While we were able to obtain a good clinical result in one patient, in another, while improvement in the diastolic pressure did result, the patient died suddenly after a few days. Autopsy disclosed that the greatly dilated aorta seen at operation had become considerably shrunken during the postoperative period of circulatory depression, so that the head of the "polliwog"





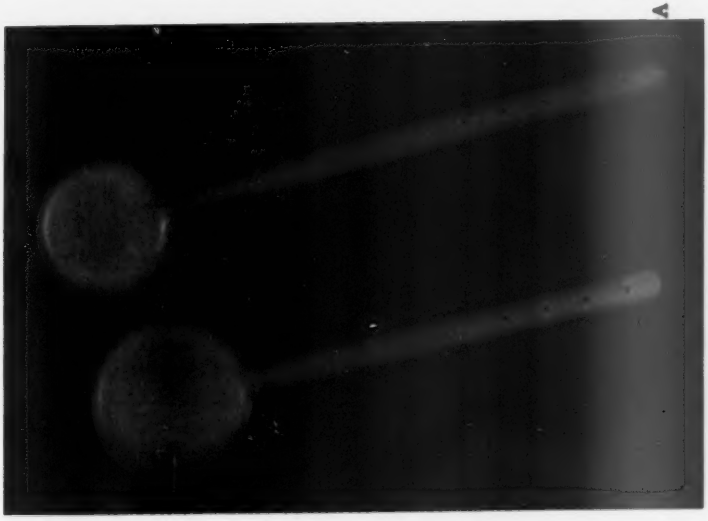


FIG. 11. A. Early Neuman valve. B. Sectional view of seated Neuman valve. C. Head of Neuman valve tends to approach and rest against internal aortic wall, thereby losing its power to function. D. Improved Neuman valve with a "shoulder." This valve cannot creep toward the internal aortic wall.

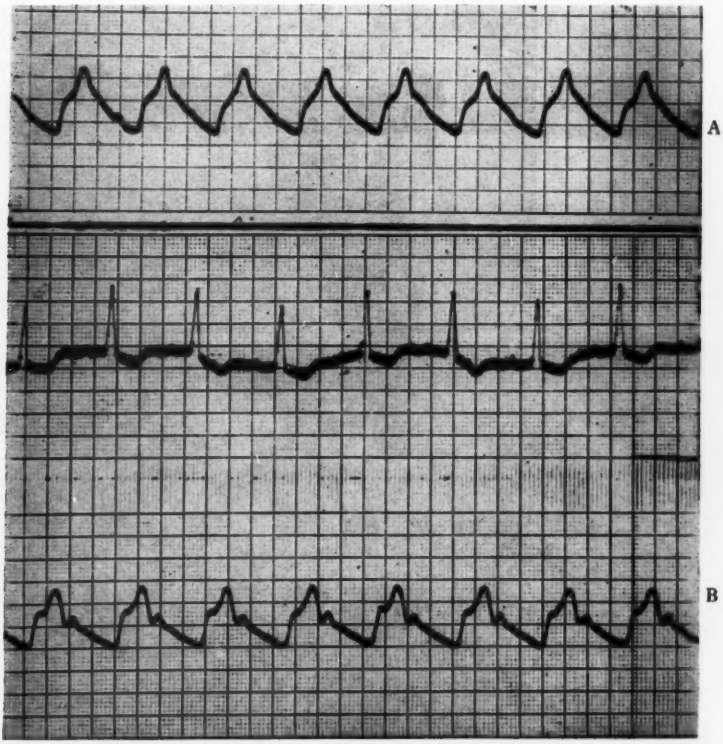


FIG. 12. A. Direct aortic arterial pressure tracing before placement of Neuman valve. B. Direct aortic arterial pressure tracing after placement of Neuman valve.

had obstructed the flow of blood through the aorta just above the level of the sinuses of Valsalva.

In this connection, it is well to consider the particular configuration of the first portion of the aorta. It closely resembles the hood of a cobra, as shown in figures 9 A and B. One can envision that a mass or sphere tolerable within the aortic lumen at the level of the valve annulus readily could become obstructive at the constricted area just above the sinuses of Valsalva.

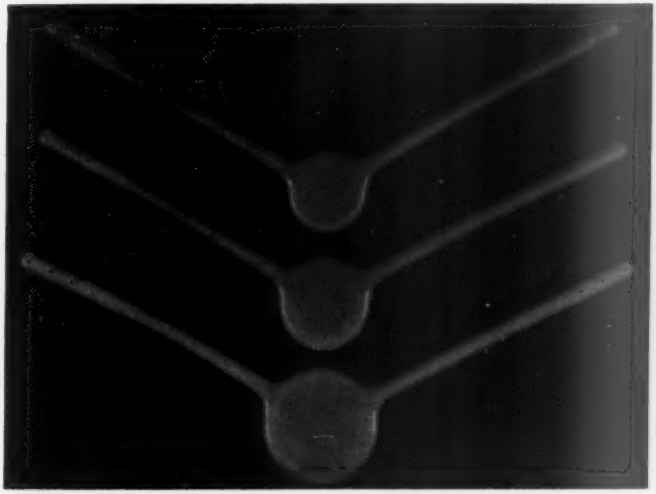
In the belief that a perfectly smooth structure such as a sphere of silicone rubber might be preferable to a soft mass of nylon, because of its relatively unchanging shape and because this substance is non-wettable and repellant to clotting, such improved "polliwogs" * were designed and developed in several sizes. These have become known as Neuman valves (figure 10).† However, the knowledge that a sphere of the size required to tamponade an

* These and the subsequently mentioned silicone rubber flap valves were manufactured for us by the Stalwart Rubber Co., of Bedford, Ohio.

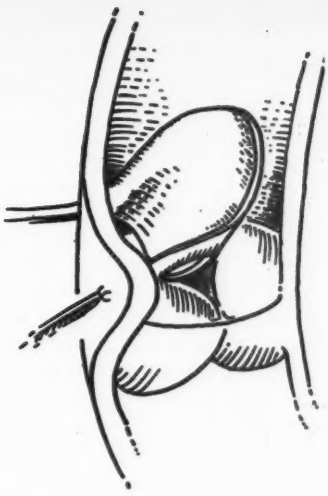
† Because of the generosity of the Neuman family in supporting this research.

opening which is basically triangular in outline might obstruct the aorta above the valve level deterred us from applying them in a human subject.

Flat discs of silicone rubber with flattened "tails" were then designed in various sizes (figure 11 A). It was felt that such a flat disc would "seat" itself over the triangular opening and tamponade it more effectively than



A



B

FIG. 13. A. Two-tailed disc. B. After placement in aortic valve the elastic tails held disc at such an angle that it could not function.

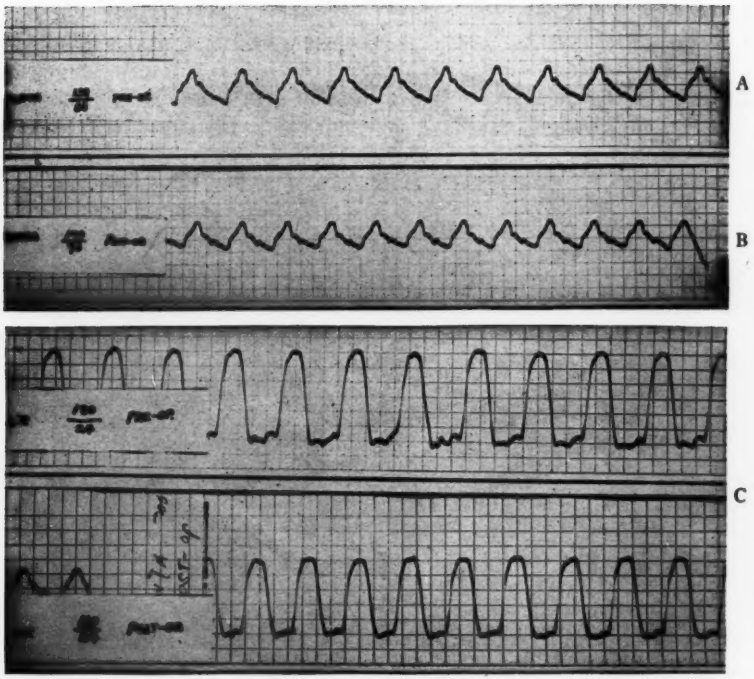


FIG. 14. A. Direct aortic pressure curve before placement of two-tailed nylon ball. B. Direct aortic pressure curve immediately after placement of two-tailed nylon ball. C. Ventricular pressures before and after insertion of valve.

would a sphere (figure 11 B). Two-tailed discs were also prepared. However, tests in animals convinced us that the disc would progress toward the aortic wall until it came into contact with it and would then lose its ability to function (figure 11 C).

It was therefore necessary to create a shoulder on the "tail" which would hold the disc away from the internal aortic wall (figure 11 D). Such a shouldered disc was placed in the aorta of a young woman with severe aortic regurgitation whose preoperative blood pressure averaged 150/0 mm. Hg. As soon as the prosthetic valve was placed a significant change in the arterial pressure tracing was noted (figure 12 A, B). The valve could be felt to function both by the fingertip in the aorta and by external palpation over the surface of the aorta and ventricle. The blood pressure taken at the conclusion of the operation averaged 120/50 mm. Hg. However, a diastolic murmur remained audible.

A two-tailed disc (figure 13 A) was placed in the aorta of a young male with severe aortic regurgitation. However, there was unexpectedly severe hemorrhage during the course of the operation, which led to severe hypo-

tension and the necessity for massive blood transfusions. Renal shut down developed and he died on the tenth postoperative day.

It was felt that the disc had not functioned well postoperatively, and had remained at an angle oblique to the aortic stream (figure 13 B). This was apparently related to the elasticity of the silicone rubber tails.

As a result, a different type of valve was prepared. It was reasoned that if one was created with completely flaccid tails the head would follow the course of flow of the blood, moving up during systole and down during diastole. If the tails were not too long and were two in number, the oscillation of the head of the prosthesis would be restrained to a limited arc and it would be unable to rise high enough to block the upper aortic passageway during systole. Furthermore, if the head was manufactured of material that was soft and malleable it would in time "mold" itself to fit the triangular valve orifice more nearly perfectly. It would be definitely superior to the sphere of fixed shape, which can never accurately block a triangular aperture, and even to the flat disc, which can never seat itself accurately upon a surface if even the slightest irregularity exists.

For these reasons, we have finally returned to the ball of nylon mesh, but suspended by two tails. This material apparently does not cause thrombosis, and remains strong and flexible in fluid with the pH of blood indefinitely. This has been placed in the aorta of two individuals with a remarkable change in the level of the diastolic blood pressure. The changes in the direct aortic and left ventricular pressure tracings are shown in figures 14 A, B, C.

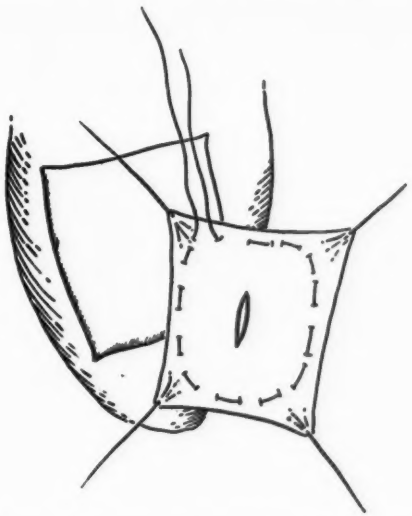


FIG. 15. "Poncho" of pericardium prepared from anterior portion of sac.

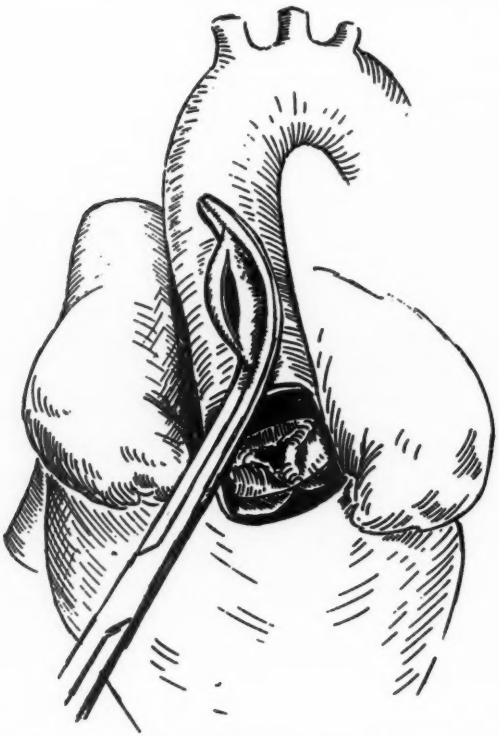


FIG. 16. Excluding a portion of the ascending aorta. An incision 4 cm. in length is made.

SURGICAL TECHNIC

The patient is operated upon in the supine position and an anterior transverse thoracic incision is made at the level of the fourth interspace curving below the breasts in the female. The right third and the left fourth interspaces are opened. Both pairs of internal mammary vessels are divided and ligated. Both fourth costal cartilages are divided and the sternum is transected at the level of these cartilages. This provides an excellent exposure to the precordium.

The major portion of the anterior and left side of the pericardium is resected in a single large sheet. An incision 4 cm. in length is made in the center of this pericardial patch. A purse-string suture is placed about the periphery of the patch (figure 15). This creates a "poncho."

The most prominent portion of the wall of the ascending aorta is picked up with fine hemostats and a generous portion is excluded from the main stream, using a special excluding clamp (figure 16). A 4 cm. incision is

made in the center of this excluded portion and the incision in the "poncho" is accurately sutured to the aortic incision, using an overlapping or imbricating technic (figures 17 A, B).

The pouch of pericardium is flushed with heparin solution and filled with saline. The ends of the purse-string suture are incorporated within a Rumel-Belmont tourniquet. The operator inserts his ungloved left index finger into the pouch, the tourniquet is tightened, and the excluding clamp is removed from the aorta. If any bleeding occurs about the finger, an unrolled gauze sponge may be wrapped about the pouch and tightened sufficiently to restrain it.

The finger explores the valve and determines the type and extent of the pathology. If any aortic stenosis coexists, an attempt is made to split the commissures with the finger. This is possible in over half of all cases with aortic stenosis. In patients with more resistant valves, the retrograde aortic dilator is passed into the pouch along the finger and is guided by it through

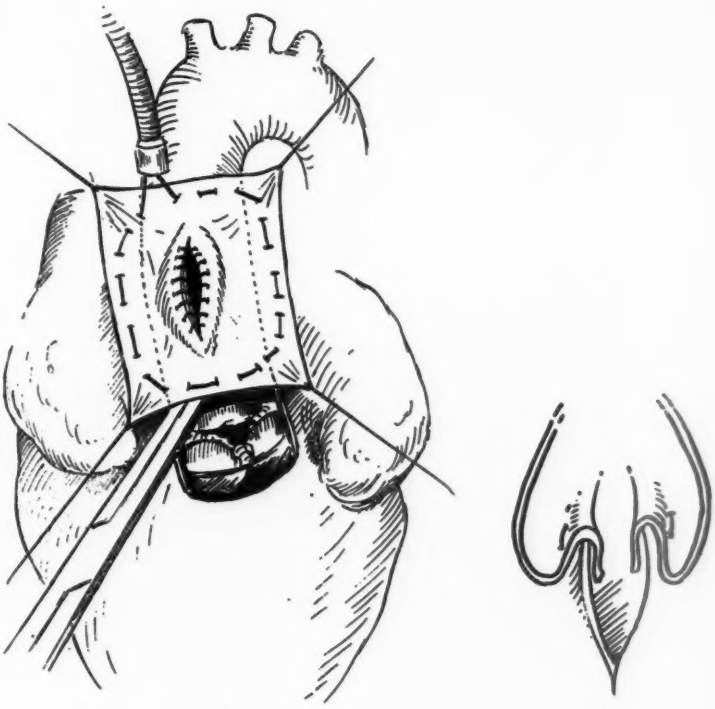


FIG. 17. A. Suturing of opening in poncho to incision in aorta. B. Sectional view to show overlapping technic.

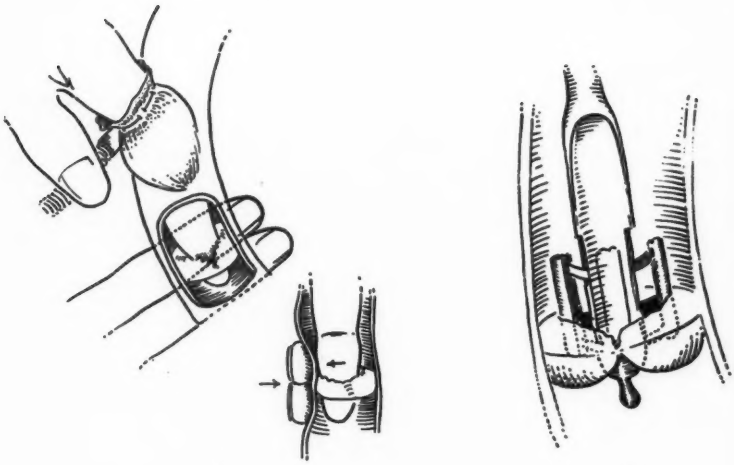


FIG. 18. A. Digital commissurotomy of the aortic valve. Counter pressure may be applied to aid in the splitting. B. Instrumental commissurotomy of the aortic valve. The finger along the posterior aspect of the dilator guides the commissural separation and limits its extent.

the valve orifice to force the commissural separation instrumentally (figures 18 A, B).*

When the valve is one with coexistent stenosis, after completing the aortic commissurotomy preparations are made to place a nylon valve above the site of leakage.

A curved surgical probe threaded with nylon suture material at its tip is passed along the intra-aortic finger and is guided through the right anterior sinus of Valsalva just alongside the anterior valve commissure. The probe tip emerges from the overlying right ventricle and the suture it bears is grasped.

The probe is withdrawn, rethreaded and repassed. It penetrates the right posterior sinus of Valsalva, emerging into the chamber of the right atrium and then piercing its lateral wall or appendage. Again the suture is grasped and the probe is removed.

These two sutures emerging from within the aorta are now attached to the tails of the nylon tampon. By traction upon the opposite ends of the sutures the ball is drawn into the aorta, tension on the tourniquet being loosened momentarily for this purpose. The ball descends to the valve level and begins to move with the blood currents. The exact placement and the extent of the arc of its mobility are adjusted by traction upon the tails or loosening by the intra-aortic finger. When it is felt that maximal function

* Obtainable from G. P. Pilling Sons, Inc., Philadelphia.

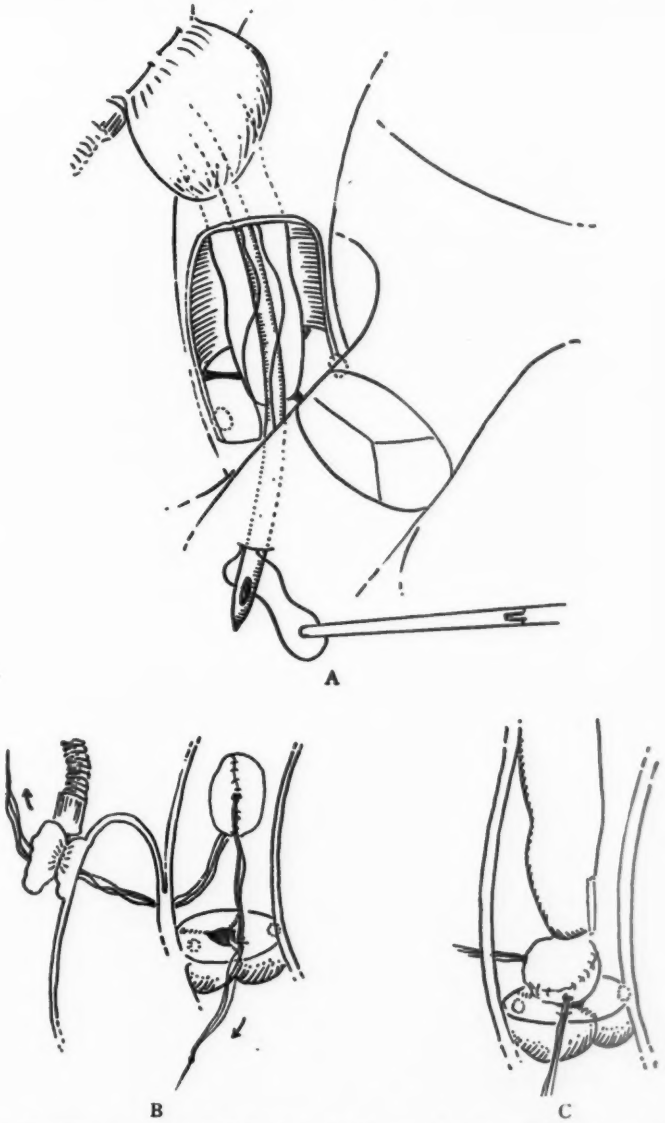


FIG. 19. Placement of two-tailed valve. A. Passage of probe anteriorly to emerge from the right ventricular outflow tract on its anterior surface. B. Drawing nylon tails through aortic wall and out of surface of the heart. Posterior tail emerges from the aorta to traverse the right atrial chamber. C. Adjustment of location and mobility of prosthetic valve by guidance of intracardiac finger.

has been achieved, the tails are brought through silicone discs and are tied securely in position (figures 19 A, B, C).

On the other hand, when the insufficiency is associated with normal valve cusps and a dilated annulus, the finger temporarily is removed from the aorta to permit application of a constricting sash about the annulus. The aortic opening is temporarily reclamped with the excluding forceps.

Purse-string sutures are placed about the bases of both appendages and both are clamped preparatory to insertion of the operator's fingers into their lumina. The tips are opened and cleansed with saline. First, the operator's right index finger is inserted into the left auricular appendage, and then the left is inserted into the patient's right appendage.

After exploring the mitral valve and correcting any coexisting mitral stenosis or recognizing any mitral insufficiency for future reference (possible corrective surgery at another operative session), the interatrial septum is explored. The lowest extent of the intracardiac aorta is recognized. Then, an assistant passes a curved, malleable probe, threaded at its tip with heavy nylon suture material, along the operator's right index finger into the left atrium. The operator guides the passage of the probe until its tip comes to rest against the interatrial septum at a point close to the aortic wall and just above the lowermost extent of the aorta. The assistant presses the probe onward so that its tip enters the right atrium. Here, it is palpated by the left index finger and is guided along it to emerge from the right auricular appendage. The suture borne in the tip is grasped and the probe is removed from the heart.

A nylon sash 30 inches in length and 4 inches wide is cut to taper at either end. One tapered end is attached to the suture emerging from the

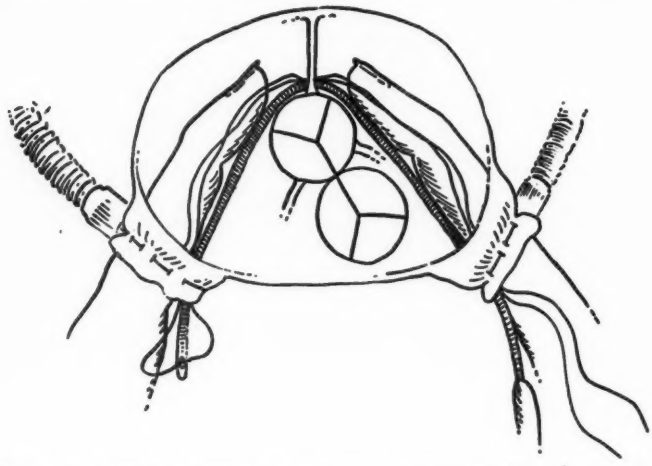


FIG. 20A. Passage of malleable probe through interatrial septum, top view.

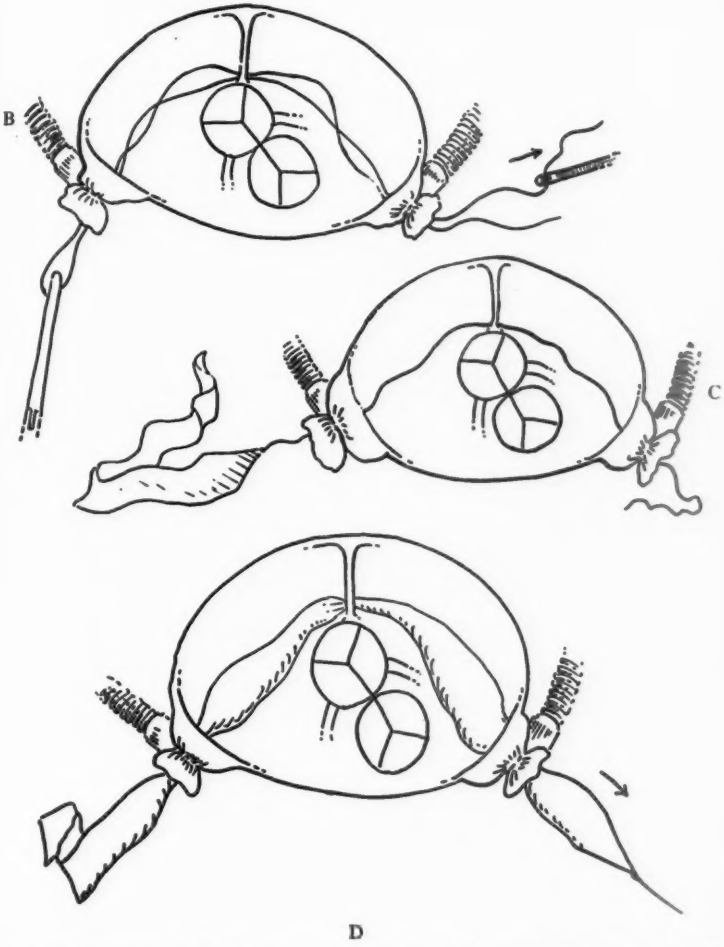


FIG. 20. (*continued*) B. The suture is grasped and the probe withdrawn. C. Nylon sash is attached to emerging right atrial suture. D. Sash drawn completely through both atria and septum.

right auricular appendage. By traction upon the suture end emerging from the left appendage, the end of the nylon sash is caused to traverse both atrial chambers and the intervening septum and to emerge from the left appendage (figures 20 A, B, C, D).

The main pulmonary artery is dissected free of the aorta to its base. Starting at the most apical portion of this separation, a threaded probe is forced through the ventricular musculature, well under the right coronary

FIG. 21. A. The pulmonary artery and aorta are dissected apart. The left coronary artery is not always visualized in the living patient. B. Threaded probe is passed deep to the right coronary artery to enter the right atrium and emerge from the appendage. C. Drawing nylon sash along course of probe passage.

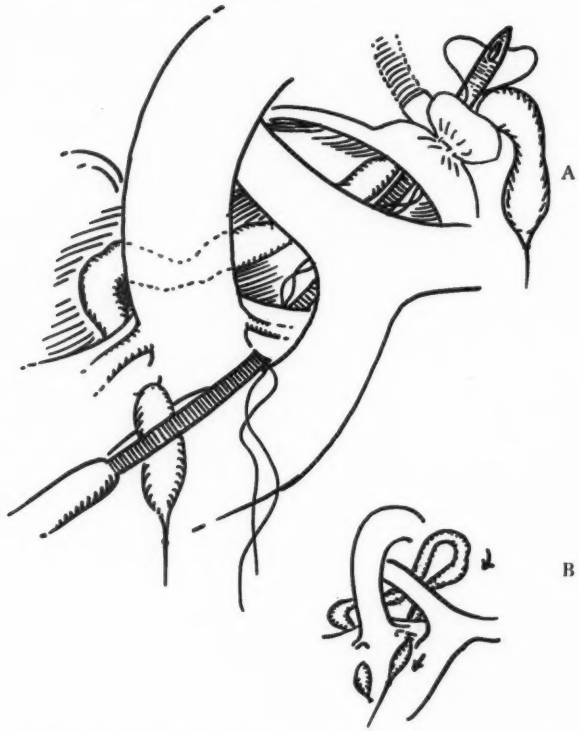


FIG. 22. A. Threaded probe passed between aorta and pulmonary artery under left coronary artery to enter left atrial chamber and emerge from appendage. B. Drawing left side of sash along course of probe.

artery, until the tip enters the right atrial chamber. The sutures are grasped as the probe tip emerges from the right auricular appendage. The probe is withdrawn.

The suture is now attached to the trailing end of the sash and is drawn back along the course of passage of the probe until the sash emerges from the anterior surface of the heart close to the root of the pulmonary artery (figures 21 A, B, C).

Another threaded probe is passed between the separated aorta and the pulmonary artery, dips deliberately beneath the left coronary artery, which is readily recognized by palpation, and enters the left atrial chamber high up so that it cannot encroach upon the left ventricular outflow tract. The

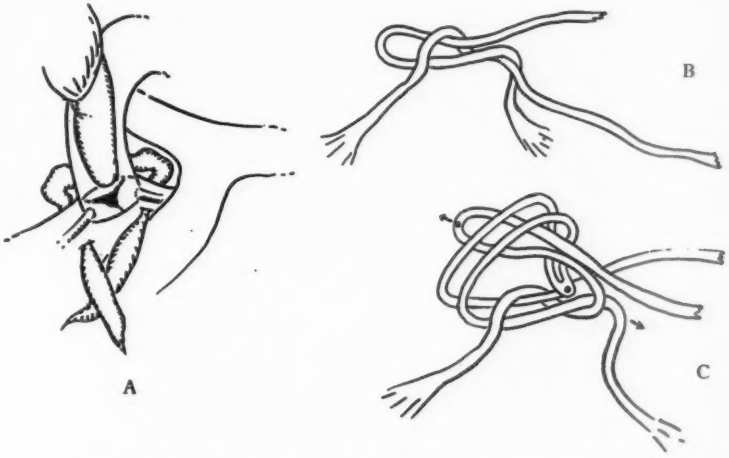


FIG. 23. A. As an experienced assistant holds a guiding finger in the aorta the sash is tied down, using a special bow-knot which can be completely released at any time. B. Special bow, first throw. C. Special bow, second throw.

tip emerges from the left auricular appendage and again the suture is grasped. The probe is removed.

The suture end emerging from the left auricular appendage is secured to the end of the nylon sash and this is drawn back into the left atrium under the left coronary artery and out between the aorta and pulmonary artery (figures 22 A, B).

An experienced assistant now places his left index finger through the pouch into the aortic lumen to guide the tightening of the nylon strip. This latter is tied in a special bow knot (figures 23 A, B, C), which permits rapid untying, if required.

The knot is tightened somewhat more than seems necessary to restore valve competence, since there is always some loosening of the constriction

during the first 24 hours. In a properly indicated case, valve competence is usually fully restored by reducing the cross-sectional area of the aorta by one-half.

Then, the procedure is terminated by clamping and suturing the aorta, closing the appendages, and reconstructing the chest wall.

Occasionally a patient is seen in whom both types of incompetency are seen. In him, both procedures would seem indicated.

Summary

1. Aortic insufficiency may be an extremely serious valvular defect, resulting in significant changes in circulatory dynamics which are often incapacitating or fatal.

2. Two entirely different types of acquired cardiac pathology occur which are capable of causing serious aortic insufficiency. An entirely different type of surgical treatment is indicated for each condition. Technical methods suitable for each have been worked out in the dead heart and in experimental animals. Both operative technics now are apparently sufficiently perfected for application in seriously ill human patients.

3. Various types of pericardial and plastic prosthetic valves have been placed in the beginning of the aorta in human patients. There have been two deaths and five survivors since the nylon and silicone rubber prostheses were developed. Four of the survivors have shown evidence of objective benefit, with elevation of the diastolic blood pressure, characteristic changes in the arterial pressure wave, and diminution of the other characteristic evidences of the disease.

4. Surgical constriction of the aortic root close to the annulus has been applied in five patients, with two deaths and two clinical improvements.*

Conclusions

These surgical efforts to correct aortic insufficiency have been applied to patients who were seriously ill with a dynamic lesion. However, this has been a pioneering effort, and it was considered unwise to subject any patient to the rigors and risks of a new technic unless he was already reduced to the terminal phase of his disease without possibility of medical salvation. Unquestionably, the advanced clinical state of the patients had a direct bearing on the operative mortality. Under equally adverse circumstances the worth of mitral and aortic commissurotomy and mitral commissurorrhaphy was established and the basic principles were clarified so that these technics could be more universally and effectively utilized.

The rather remarkable and immediate improvement obtained in some of these patients (figure 24) encourages us to feel that we are at last on the

* Since the presentation of this manuscript 18 more patients have been operated upon by these technics. There have been three operative and two late deaths. Most of the survivors have shown marked benefit.

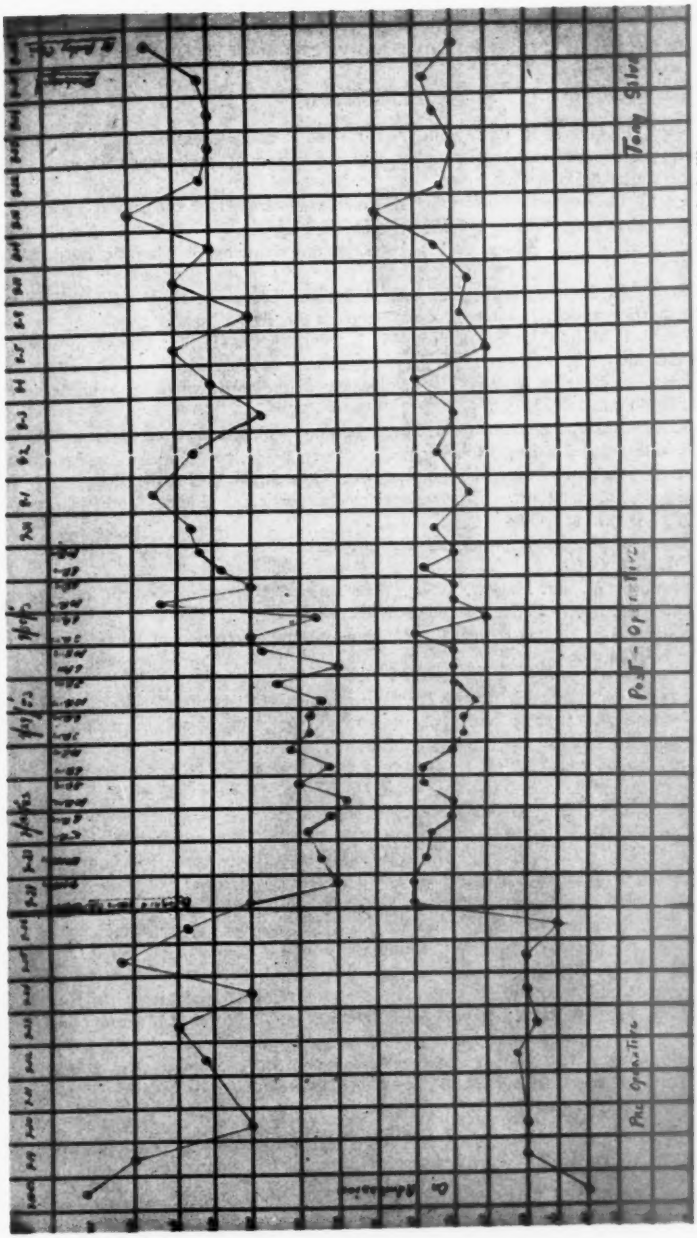


FIG. 24. Daily blood pressure chart in T. S., showing changes due to surgery (single-tailed nylon fabric ball). This benefit has now persisted for 18 months.

right course. Perhaps it will soon be possible to add aortic insufficiency to the growing list of cardiac lesions readily responsive to surgical intervention.

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CASE REPORTS

FATAL TOXIC ENCEPHALITIS OCCURRING DURING IPRONIAZID THERAPY IN PULMONARY TUBERCULOSIS *

By ROGER S. MITCHELL, M.D., F.A.C.P., *Trudeau, N. Y.*

IPRONIAZID (the isopropyl derivative of isonicotinic acid hydrazine, "Marsilid" †) was first made available for trial in patients with tuberculosis in June, 1951.[1] During the first six months of its use iproniazid was found to be less tuberculostatic than isoniazid in vitro,[2] but possibly more effective in relieving tuberculotoxicity than isoniazid in vivo.[1, 3] Untoward effects were much more common with iproniazid than with isoniazid.[1, 3, 4, 5, 6, 7] While the drug has now been withdrawn from any use in patients because of these side effects, especially of the central nervous system,[3, 5, 7, 8] no deaths attributed to iproniazid have as yet been found in the literature. At least one death from isoniazid (dosage up to 20 mg./Kg.) with symptoms and signs suggestive of toxic encephalitis has been reported.[9]

This case may represent an instance of fatal iproniazid toxicity.

CASE REPORT

A 60 year old physician was re-admitted to Trudeau Sanatorium on September 18, 1951, complaining of dyspnea, cough, expectoration and weakness of several years' duration. He had been well until 1921 when, at the age of 29, a chest roentgenogram showed bilateral "inactive" disease. This finding was ignored and the patient continued to lead an active life. His general health was only fair. He was constantly below his normal weight, his appetite was capricious, and he suffered at times from hunger pains relieved by milk or soda. In 1925 a diagnosis of duodenal ulcer was made and a modified ulcer régime was followed until 1933.

In January, 1933, following a heavy chest cold, he had a chest roentgenogram which showed extension of disease. He then spent six months at Trudeau Sanatorium, from February to August, 1933, on modified bed-rest. Sputum was intermittently positive for acid-fast bacilli throughout his stay. While he continued to have some cough and expectoration, these symptoms were mild until 1937. By this time chest roentgenograms showed bilateral increase of disease. He spent an additional six months (June, 1937, to January, 1938) on modified bed-rest at Trudeau Sanatorium. Sputum was again intermittently positive throughout his second stay. After working part-time for about two years he resumed his practice for eight hours a day. He was then fairly well and able to work for six years. Increasing dyspnea was noted, however, and sputum smears were positive during this period.

* Received for publication September 20, 1954.

From Trudeau Sanatorium of the Trudeau-Saranac Institute, Trudeau, N. Y.

† The iproniazid (1-isonicotinyl; 2-isopropylhydrazine) used in this case was kindly provided by Hoffmann-LaRoche, Inc., Nutley, N. J.

In March, 1946, following a severe respiratory illness, extension of disease with left upper lung cavity was noted. Because of disagreement on interpretation of films he continued working but with increasing cough, expectoration and dyspnea. During this period there were, in retrospect, several further slight extensions of disease. In May, 1950, he took 8 gm. of para-aminosalicylic acid (PAS) daily, and two months later added streptomycin, 1 gm. intramuscularly, twice weekly. He continued at work while taking both drugs until August, 1951, when he was reëxamined at Trudeau Sanatorium. Planigrams confirmed the presence of a 3 by 4 cm. cavity in the left infraclavicular region. Sputum was highly positive by both smear and

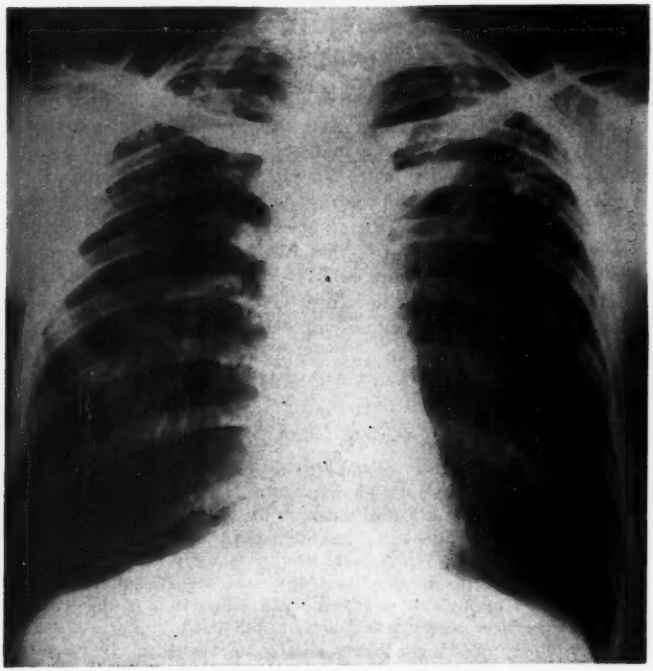

FIG. 1. Chest roentgenogram on admission, September 20, 1951, shows bilateral old fibroid tuberculosis with cavity in left infraclavicular region.

culture. The tubercle bacilli were found to be slightly resistant to streptomycin and moderately resistant to PAS in vitro. Past, family and social histories and a review of systems were noncontributory.

On admission the following month he was a thin, slightly pallid, chronically ill appearing middle aged man with moderate dyspnea on mild exertion and a rather frequent cough productive of about 1 ounce of mucopurulent sputum in 24 hours. Breath sounds in both lungs were diminished, and the expiratory phase was prolonged. Some coarse râles were heard in both upper lung fields, more on the left. The examination was otherwise noncontributory.

The admission chest roentgenogram (figure 1) showed nodular and stringy densities throughout the upper half on the right and upper two thirds on the left,

with a 3 by 4 cm. cavity posteriorly located under the left clavicle, confirmed by planigram.

Blood counts and urinalyses were within normal limits. Maximum breathing capacity was 35 L./min., in contrast to a predicted value of 118 L./min.; there was no improvement after inhalation of a bronchodilator. Residual air was 3.91 L., with a predicted value of 1.38 L., and represented 60% of the total volume. (These are the classic findings of diffuse obstructive emphysema.)

He was placed on a régime of bed-rest for about 19 to 20 hours a day. Pneumoperitoneum was induced on September 21, 1951, and continued with weekly refills of 500 to 750 c.c. until just before his death. Streptomycin dosage was changed to 0.5 gm. intramuscularly daily, and PAS to 12 gm. per day on October 2, 1951. There was some improvement in cough and expectoration and slight reduction in the size of the cavity and in the number of bacilli noted on concentrated smear. Maximum breathing capacity was 27 L./min. on November 19, 1951; 26 L./min. in March, 1952, and 19 L./min. in May, 1952. Residual air showed no essential change.

In early December, 1951, the patient left the sanatorium but continued at home the same program as to partial bed-rest, diet supplements, drug therapy and maintenance of the pneumoperitoneum. A slow gain of 10 pounds in weight was achieved, but no significant increase in strength and no improvement in his dyspnea on exertion. The patient was afebrile. Cough and sputum production were moderate.

It is of interest, in view of later events, that the patient was subject, as he had been for many years, to occasional attacks of abdominal cramping pain which were apt to be followed by brief diarrhea. These symptoms were attributed to an irritable colon. For relief he occasionally took Demerol, with benefit and no untoward symptoms.

During February, 1952, favorable reports on the use of isonicotinic acid preparations determined the patient's return to Trudeau Sanatorium for a trial of iproniazid therapy.

On March 22, 1952, he was given 250 mg. iproniazid per day (about 5 mg./Kg.). PAS was discontinued and streptomycin was continued. There was a prompt improvement in appetite, general well being, cough and expectoration, and a gain in weight in ensuing months from 123 to 153 pounds. The number of acid-fast bacilli in concentrated sputum smears dropped quite abruptly, and the number of tubercle bacilli on cultures dropped from countless colonies to from none to 15 just before discharge.

On the other hand, no particular change was noted on the serial chest roentgenograms, and the dyspnea increased slowly but steadily. In addition, soon after starting iproniazid he noted repeated bouts of spasm of the muscles of the extremities and abdomen. Tendon reflexes were exaggerated.

On April 22, 1952, about 20 minutes after receiving 100 mg. of Demerol, given to relieve recurring symptoms of "pylorospasm" and "spastic colon," he noted nausea and severe muscle twitching in the thighs. On examination there were ashen cyanosis, profuse perspiration, rise in blood pressure to 155/65 mm. of Hg, a pulse rate of 120, distended abdomen, very exaggerated tendon reflexes, bilateral ankle clonus and positive Babinski. After removal of 1,000 c.c. of pneumoperitoneum and the administration of nasal O_2 he began to improve and was restored to his former state within 36 hours.

He was discharged to his home on June 13, 1952. Streptomycin therapy was stopped but the patient continued to take 250 mg. of iproniazid daily. In addition, he followed a régime of partial bed-rest with very gradually increasing easy exercise. The pneumoperitoneum was maintained by weekly fillings.

During the three month period from the time of his return home in mid-June until the onset of his final acute illness on September 20, the patient was continued on the same dose of iproniazid; otherwise, his régime was very similar to that for

the three month period prior to his visit to Trudeau in April. The rather striking differences in the patient's condition and behavior can therefore be reasonably attributed to the effect of the drug. The most evident changes were in his mood and in his appetite. For many years the patient had been rather anxious and depressed, particularly since 1950, when he felt his physical strength failing and dyspnea becoming prominent. He had shown little ability to interest himself in anything other than his necessary work. During the period of taking the drug he became cheerful, at times to a point where the question arose whether the euphoria was not a trifle pathologic. It is true, of course, that there was a tremendous encouragement in the remarkable increase in appetite, which was the second most obvious change. On the other hand, there was little improvement in the distressing dyspnea on exertion, but even this handicap did not appear to cause the same discouragement as previously. The patient showed active interest in certain hobbies and in the discussion of medical problems.

The increase in appetite and consequent steady gain in weight were very remarkable in an individual who for the preceding 20 years at least had been notable for his difficulty in maintaining an adequate intake of food. The total weight gain on the drug was 30 pounds.

Less prominent symptoms were the presence of slight tremor in the arms and legs, accompanied by moderately hyperactive deep reflexes, but without at any time any true clonus or positive Babinski. The patient stated that there was noticeable increase in frequency of urination and some urgency. There had been marked falling off in potency for the preceding four or five years, but the patient felt that this loss was further aggravated during the period of drug administration. The patient slept rather restlessly. He complained at times during the months preceding the final illness of some tinnitus. These symptoms, suggestive of a mild toxic effect on the central nervous system, were not considered severe or troublesome by the patient. They were perhaps somewhat masked by the patient's optimistic outlook, his gradual improvement in strength, and his steady gain in weight. Weekly examinations of the urine, blood count and differential gave normal findings.

His final illness began on September 20, 1952, when he awoke with aching in the precordium and left axilla, intensified by cough and movement. This slowly increased. In the afternoon of that day his temperature rose rather abruptly to 103° F. New physical signs were absent. The patient looked ill. Under the impression that this acute febrile state with chest pain signified an intercurrent pulmonary infection, he was given 600,000 units of penicillin at once, and this was repeated daily for five days. Temperature fell abruptly during the night of September 20 and thereafter for five days did not rise above 100° F. However, the patient continued to look quite ill, lost all his appetite, was very fatigued, began to complain of headaches of mild severity at night, slept poorly and was noted to be talking constantly in his sleep, as well as twitching and jerking.

The iproniazid was discontinued on the evening of September 24. On the morning of September 26 he noted double vision. He was admitted that day to the Johns Hopkins Hospital. Neurologic examination, aside from weakness of the right external rectus muscle, was negative. Eye grounds showed slight congestion of veins, no papilledema. There was no rigidity of the neck and no Kernig's sign.

Lumbar puncture on September 27 showed clear fluid, pressure 180 mm., with a free rise and fall with jugular compression. The white cell count of the spinal fluid was 110 per cubic millimeter, with 80% mononuclears and 20% polynuclears. The fluid also contained 308 red blood cells per cubic millimeter. The Pandy test showed only a faint trace. (Cultures of the spinal fluid and animal injections were later reported as negative.) Two sputum examinations were positive for acid-fast bacilli in concentrated smears.

The hemoglobin was 13.5 gm.; hematocrit, 41; white blood cell count, 11,750,

with a normal differential count; blood nonprotein nitrogen, 30 mg.%; blood sugar, 112 mg.%; blood CO_2, 30 mEq.; chloride, 84.7 mEq.; total blood protein, 6.9 gm.; urinalysis, negative. Chest roentgenogram showed bilateral advanced tuberculous infiltration as before, but no evidence of any acute recent spread.

The patient grew increasingly more toxic and began to show some mental confusion and coarse tremor of the hands intermittently. The temperature became subnormal; pulse, 80 to 90; respirations, 20 to 24. On September 27 a hallucinatory state developed. This was chiefly visual—seeing strangers in the room, large particles of dirt floating on the ceiling, a magazine in his hands disappearing and attaching itself to the wall above the bed, and the like. There were also auditory delusions, which he interpreted as a recording apparatus which repeated everything he said after he had completed a sentence. At intervals he would become quite lucid. By September 29 and 30 his respirations had risen to 36, his pulse to 120, and his temperature to 101° F. There was marked irregularity in the rhythm of his breathing, with irregular apneic pauses. At times costal and diaphragmatic breathing were in opposition to each other. Pulse continued reasonably strong, and the blood pressure was above its usual level (110/70 mm. of Hg), reaching 140/80 mm. of Hg.

Toward evening on September 30 the coma deepened and he died.

In the early days of the patient's terminal illness the double vision, increasing headache and motor restlessness suggested the possibility of a tuberculous meningitis. This clinical impression was later altered to meningo-encephalitis.

Permission for post mortem was limited to the brain. The examination was performed by Dr. Arnold Rich.

Gross Findings: External examination of the body revealed no significant abnormalities. The brain was symmetrical and well fixed. The dura mater over the hemispheres was normal and the longitudinal sinus was empty. The major fissural pattern was normal, and there was neither convolutional swelling nor atrophy. The cerebral arteries at the base showed only an occasional small yellow plaque. No aneurysms or occlusions were found. There was no cerebellar pressure cone or evidence of uncal herniation. The meninges were everywhere thin and transparent except over the superior portions of the parietal lobes. Here numerous focal milky spots, 2 to 3 mm. in diameter, were noted in the leptomeninges.

There were three fresh subarachnoid hemorrhages, each about 1 cm. in diameter. They were located over the left superior frontal convolution, over the right postcentral sulcus, and over the left fusiform gyrus. On serial coronal sections there was good differentiation of gray and white matter. The cortical ribbon was of normal thickness in all parts. The ventricles were symmetric and not dilated or shifted. There was no evidence of ependymitis. The only lesions made out were numerous minute punctate red dots, mainly in the cortex of the parietal and frontal lobes, but also in the white matter, particularly in the occipital lobes. The thalamus and basal ganglia were largely spared. In the posterior limb of the left internal capsule was a 3 mm. punctate red area. The galenic veins and the aqueduct of Sylvius were patent.

On cross section through the superficial hemorrhagic areas described on the frontal, parietal and temporal lobes no involvement of the underlying cortex was seen. On serial coronal sections through the brain stem no gross lesions were made out until one reached the lower mesencephalon, where there were a few dilated vessels with slight brownish discoloration about them. The remainder of the brain stem was grossly normal. Sections of the cerebellum and vermis showed no gross abnormalities.

Microscopic Notes: Hypophysis: Four sections showed a normal appearing capsule and pars nervosa. The stalk present had a small fresh hemorrhage in its central portion. The basophils were vacuolated in the anterior lobe (noted in the

Mann stain). There was a small subcapsular chromophobe adenoma in the anterior lobe composed of large columnar cells arranged in loose columns and occasionally forming an ill defined papillary pattern.

Brain (15 sections studied): There was no evidence of tuberculosis in either the brain or the meninges. The grossly described meningeal patchy opacities were not striking, being composed of small focal acellular hyaline connective tissue. A sparse mononuclear cell reaction was present in small focal areas in the subarachnoid space. Occasional pigment-laden macrophages were seen here in such foci, and fresh hemorrhage was present in some of them. No significant intimal thickening of cerebral arteries was noted. The grossly described "peppering" of the gray matter in the cerebral cortex was seen to be small fresh perivascular hemorrhages. These were present, often in abundance, in the frontal, parietal and temporal cortex and in the basal ganglia and pons. Also scattered in almost all sections of the cerebral cortex and brain stem were evidences of older perivascular hemorrhages in the form of hemosiderin-laden macrophages. There was a slight infiltration of mononuclear and occasional polymorphonuclear cells about several vessels in the cortex and pons. There was hemorrhage in some of these foci, with macrophages containing phagocytized red cells. No alterations of nerve cells were seen. The sections of internal capsule showed no encephalomalacia or thrombosed vessels.

One guinea pig was inoculated with spinal fluid taken immediately post mortem, and another guinea pig with an emulsion of brain tissue obtained from autopsy. Both of these guinea pigs were still alive for two and one-half months when sacrificed; no tuberculosis was found. Smears and cultures for tubercle bacilli were also negative. Cultures of spinal fluid were also negative for fungi.

Anatomic Diagnoses: History of chronic pulmonary tuberculosis with terminal diplopia and coma. Slight focal leptomeningeal scarring. Focal subarachnoid hemorrhages. Focal perivascular fresh hemorrhages in cerebral cortex, and hemosiderin deposits about parenchymal vessels and in meninges. Slight perivascular mononuclear infiltrations associated with hemorrhage in brain stem and cerebrum. Occasional hyaline intracerebral vessels. Chromophobe adenoma, hypophysis.

Comment

It is unfortunate that a general post mortem was not available. From the brain findings and clinical course, however, there was no indication of a terminal dissemination of tuberculosis.

Virus and fungus encephalitis were considered by the pathologist in his search. Bacteriologic examination for the usual organisms and for fungi was negative. The inflammatory reaction found is considered quite atypical for an infection.

On the other hand, the patient was receiving a drug which is now known to have been toxic to the central nervous system in many patients, and which had apparently been acutely toxic to the central nervous system of this patient immediately following the use of 100 mg. of Demerol. It seems reasonable, therefore, to attribute this patient's death to hemorrhagic encephalitis due to a toxic effect of iproniazid.

There has been one other death of a patient receiving iproniazid at Trudeau Sanatorium. In this case there was no demonstrable relationship between death and the drug. A 50 year old man with moderately advanced pulmonary tuberculosis died very suddenly without any warning whatsoever on the eighth day of iproniazid therapy (4 mg./Kg.). A complete postmortem examination, in-

cluding the brain, revealed no cause for death. It was presumed that death was due to ventricular fibrillation.

There is now experimental evidence that both isoniazid and iproniazid can displace nicotinamide as a part of diphosphopyridine nucleotide (DPN) or Coenzyme I[10, 11]. DPN is essential for cellular oxidation-reduction reactions involved in carbohydrate metabolism. The isoniazid- and iproniazid-substituted analogues of DPN do not function in these reactions in the same manner as does the parent compound. In fact, they appear to be biologically inactive. It is suggested that an adequate amount of nicotinamide in tissue cells would prevent an intolerable accumulation of the inactive analogue. On the other hand, if suboptimal amounts of nicotinamide are maintained in the tissue cells before and during isoniazid and iproniazid therapy, an accumulation of the inactive analogue of DPN appears inevitable.

The difficulty in reversing the toxic symptoms attributed to the isonicotinic acid drugs, iproniazid in particular, can be attributed to the slow rate at which DPN can be reformed from the biologically inactive analogue in the presence of nicotinamide. Furthermore, while the breakdown of isoniazid analogue is about 10 times slower than its formation, the breakdown of iproniazid analogue is too slow to be measured. It follows that the effect of isoniazid or iproniazid on patients already suffering from a deficiency of nicotinamide or DPN should result in symptoms approximating an acute deficiency of nicotinamide, pyridoxine or riboflavin, with the more severe symptoms resulting from iproniazid therapy.[10]

In view of the similarity of the symptoms displayed by these patients to those resulting from *acute* vitamin deficiency,[12] the possibility exists that the two deaths reported may have occurred because of acute nicotinamide deficiency induced by iproniazid therapy.

Summary

A fatal toxic encephalitis is reported which occurred after six months of iproniazid therapy in a 4 to 5 mg./Kg. dosage. Postmortem examination was limited to the brain. Since there were no other obvious causes of toxicity or death, the probability that death was due to iproniazid given in the average therapeutic dosage must be borne in mind. A possible explanation of iproniazid toxicity is presented.

Acknowledgment

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PIGMENTED SPOTS OF THE ORAL MUCOSA, LIPS AND DIGITS ASSOCIATED WITH GASTRO-INTESTINAL POLYPOSIS *

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The complete syndrome of intestinal polyposis and melanin spots of the oral mucosa, lips and digits was first described by Jeghers [1] in 1944. However, as early as 1896 Hutchinson [2] reported unusual black pigmented spots on the face and oral mucosa of twins, and Weber [3] in 1919 reported that one of these twins died of intussusception at the age of 20. Peutz [4] in 1921 demonstrated a familial incidence of this syndrome by finding both pigmentation and intestinal polyposis affecting several members of the same family. He apparently did not believe that there was an important association between the two components of the syndrome as we know it today. More evidence that the syndrome was frequently hereditary was presented by Foster [5] in 1944 when he described intussusception of the small bowel, apparently caused by polyps, in a father and daughter, both of whom had dark pigmented spots of the lips and face. In 1949 Jeghers et al.[6] added 10 cases having the complete syndrome, and after reviewing the literature were able to assemble a total of 22 proved cases. Tanner [7] added another in 1951. Since then five additional cases have been reported (Schaffer and Sachs,[8] Wolf,[9] Kitchin [10] (two cases), and Kaplan and Feuchtwanger,[11] bringing the total number found in the world literature to 28.

The essential feature of the syndrome is the association of pigmented spots

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about the buccal mucosa, lips and elsewhere on the face, and often the digits, with gastrointestinal polyposis. The pigmentation differs from ephelides, or "freckles," in that it is concentrated about the mouth rather than over the bridge of the nose, and the pigmented spots are invariably found in the buccal and labial mucosa in this syndrome, while freckles are rarely if ever found in this area. The pigmentation can be distinguished from that occurring in Addison's disease in that in no instance yet reported has it been found to be generalized over the whole body or accentuated in the body folds. Lentigines differ in that they are usually widely disseminated and show no predilection for the buccal mucosa. In the reported cases of Jeghers' syndrome there has been no mention of developmental abnormalities of the nervous system, muscles, bones and skin such as occur in multiple neurofibromatosis. In all instances the patients have reported the perioral pigmented spots to have been present since birth or early childhood. All of the patients with one exception were

FIG. 1. Pigmented spots on lips and adjacent skin.

of a dark complexion. The other essential component—gastrointestinal polyposis—most frequently involved the small intestine but in many cases was generalized, affecting stomach and large bowel as well. The symptoms are mainly of small bowel origin; most commonly the condition presents itself as recurrent intussusception during the second decade of life. The polypi are usually benign, but in one case malignant change was demonstrated by pathologic examination. Gastrointestinal bleeding or unexplained anemia has not been constantly reported in this syndrome, being found in less than one third of the reported cases. A familial occurrence of the condition has been conspicuous but far from constant, being described in about one-half of the cases.

CASE REPORT

A 14 year old white schoolgirl was admitted to Simpson Memorial Institute, University Hospital, on August 3, 1953, because of an anemia of undetermined etiology.* For 15 months prior to her admission she had complained of recurrent

*The patient was referred by her attending physician, Dr. Thomas McKie, Sault Ste. Marie, Michigan.

FIG. 2. Pigmented spots on the tongue and oral mucosa.

episodes of pallor, weakness, shortness of breath and cramping abdominal pain. She had been in apparently good health until March, 1952, when she suddenly began to complain of cramping epigastric pain, anorexia, myalgia and constipation. For the first time her mother noted that she was markedly pallid. She was treated with penicillin for what was thought to be influenza, but remained in bed for one month because of persistent weakness. She then returned to school but continued to complain of extreme weakness, exertional dyspnea, palpitation and "foggy" vision. Because of these symptoms she was admitted to a hospital in April, 1952, and a diagnosis of nutritional anemia was made after finding a hemoglobin value of 6 gm. per 100 c.c. of blood and a red cell count of 3,200,000 per cubic millimeter. She was treated with "blood capsules" but no transfusions, and discharged after one month. By the fall of 1952 she was well enough to return to school, and remained asymptomatic on restricted activity. In November, 1952, she again suddenly began to complain of an upset stomach, with cramping pains, belching and anorexia. She became very pale and too weak to ambulate. She was taken to another hospital, transfused with two

FIG. 3. Pigmented spots on the fingers.

pints of blood and discharged after a few days. Again, in February, 1953, hospitalization was required for similar complaints and three transfusions were given. For the next four months the patient was asymptomatic and during this time had frequent blood counts, all of which were apparently normal. On July 1, 1953, the abdominal pains recurred, accompanied by gurgling sounds. The pain waxed and waned and was relieved temporarily by belching. She became very pale and weak and was hospitalized again. Her hemoglobin at that time was 6 gm., the red cell count 2,000,000, and the red cells were noted to be normocytic and hypochromic. Stools were negative for blood. Except for pallor and a peculiar pigmentation to be described, the physical examination was negative. Roentgenograms of her stomach, small intestine and colon were reported as negative. She was given two transfusions and discharged after 10 days. Since then and up to the time of her admission to the Simpson Memorial Institute she had felt rather well, but continued to have ease of fatigue and shortness of breath after exertion.

FIG. 4. Roentgenographic filling defects in stomach suggestive of polyposis.

FIG. 5. Polypi of stomach demonstrated by double contrast.

She has always denied bleeding from any orifice, bruising tendencies, jaundice, melena, weight loss or fever.

Dr. J. V. Neel, Associate Geneticist in the Institute of Human Biology and Associate Professor of Internal Medicine, University of Michigan, conducted a genealogic study and was unable to obtain evidence of either pigmentation or gastrointestinal disease suggestive of Jeghers' syndrome in other members of the patient's family.

On examination at this hospital she was found to be a somewhat underdeveloped, apprehensive girl with dark rings under her eyes who appeared mildly, chronically

ill. She was not noticeably pallid. Her temperature was 99.0° F.; pulse rate, 92; blood pressure, 120/70 mm. of Hg; respiratory rate, 20. Her hair and irides were brown. On the dental and vermilion surfaces of her lips and adjacent skin there were numerous flat, irregular, darkly pigmented brown spots varying in size from a

FIG. 6. Polypi of proximal jejunum demonstrated by double contrast.

pinhead to 8 mm. in diameter (figure 1). Similar pigmented spots were noted up to 18 mm. in diameter about her buccal mucosa, tongue and hard palate (figure 2), and a few on the extensor surfaces of the fingers (figure 3) and toes. This pigmentation had been present as long as the patient and her mother could recall. (Two similar brown spots were noticed on the mother's lower lip but none on three siblings examined.) The patient's breasts were well developed for her age, and pubic and axillary hair, though sparse, was present. Otherwise the entire physical examination was unremarkable.

Laboratory Data: Laboratory studies on admission revealed a hemoglobin of 10.7 gm., with 4,600,000 red blood cells and 5,150 white blood cells. The hematocrit was 41%, mean corpuscular volume 89 cu. microns, and mean corpuscular hemoglobin concentration 26%. The differential leukocyte count was within normal limits. Thrombocytes were within the normal range, and the reticulocyte count was 1.6%.

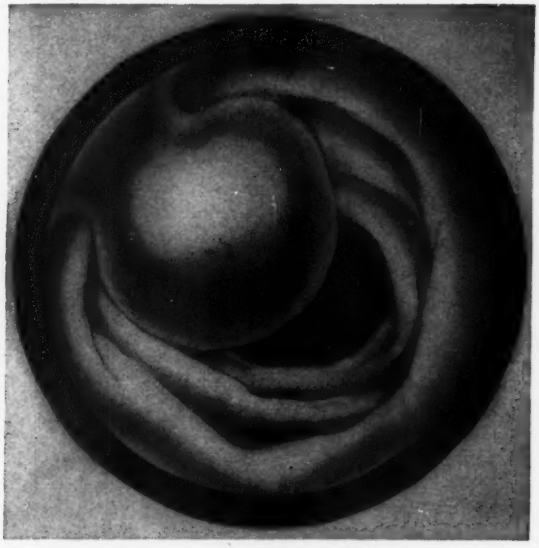

FIG. 7. Gastroscopic appearance of semi-pedunculated gastric polyp.

Direct and indirect Coombs' tests were negative. Urinalysis was negative except for occasional white cells. The sedimentation rate was 5 mm. per hour (Wintrobe); Kahn test for syphilis was negative; fasting blood sugar was 65 mg.%, and liver function tests were within normal limits. Tuberculin skin tests were negative. Guaiac tests for occult blood in the stools on four occasions were 1 plus, 0, 1 plus, and trace. A gastric analysis in the fasting state revealed 22 degrees of free acid and 15 degrees of combined acid; the contents gave 1 plus guaiac and 4 plus benzidine reactions for occult blood. On sigmoidoscopy no abnormality could be visualized up to 25 cm. Chest x-rays were negative, as was a barium study of the colon.

Fluoroscopy and x-ray studies of the upper gastrointestinal tract following a barium meal showed a large filling defect, 2.5 cm. in diameter, along the mid portion of the lesser curvature, and two smaller filling defects were noted in adjacent areas suggesting polyposis of the stomach (figure 4). With special technic, using

Rugar as the only opaque material and following with a carbonated beverage for the purpose of releasing carbon dioxide to provide double contrast circumstances, numerous varying sized filling defects were revealed within the stomach and proximal jejeunum (figures 5 and 6). These were considered by Dr. F. J. Hodges, chairman of the Department of Roentgenology, to represent polypi of these regions. Gastroscopy confirmed the roentgen impression of polyposis, as numerous polypi varying in size from about one eighth inch to one and one-half inches in diameter were visualized. The smaller ones were sessile, the larger ones semi-pedunculated and deep red in color, indicating vascularity; one medium-sized polyp had a small hemorrhagic spot (figure 7*).

Course in Hospital: Throughout her hospital stay the patient remained asymptomatic. For her mild anemia she was treated with ferrous sulfate and by the time of discharge, 14 days after admission, her hemoglobin had risen to 11.6 gm. and the reticulocyte percentage was 4. Since the gastrointestinal polyposis was believed to be so widespread and the patient was without symptoms, it was decided that no definitive surgical treatment was indicated.

Discussion

This patient demonstrated many of the already classic components of the syndrome as described by Jeghers. She had melanin spots in the areas most commonly affected in others in whom a similar diagnosis had been made, namely, the lips, buccal mucosa, fingers and toes. The pigmentation had been present since early life. She had a rather dark complexion, including brown hair and irides. The onset of gastrointestinal symptoms began during her second decade of life. These symptoms, no doubt, were in part secondary to gastrointestinal bleeding, but the history of loud gurgling bowel sounds accompanying some of the more severe epigastric pains suggests that she might well have had mild recurrent, reducible intussusception. As has been reported in other cases, the presence of small intestine polyposis was demonstrated in this patient. This case differs from others in that anemia was the chief and presenting difficulty on each of her four hospitalizations. Also, in previously reported cases, the complete syndrome was diagnosed almost invariably following laparotomy for an acute surgical abdominal emergency. Our patient's symptoms have never as yet been of sufficient magnitude to require consideration of surgical intervention. Lastly, we have been unsuccessful in attempts to demonstrate occurrence of the syndrome in this patient's family.

Summary

1. A case is reported of the syndrome of gastrointestinal polyposis and melanin spots of the oral mucosa, lips, fingers and toes (Jeghers' syndrome) in a 14 year old female.

2. The finding in this patient of the typically distinctive melanin spots associated with gastrointestinal polyposis as demonstrated by x-ray and gastroscopy provides further evidence that the syndrome is a distinct entity.

3. Attention is called to this patient's chief complaint, anemia. Hence, anemia in a patient having the pigmentation described above, with or without

*Drawing by Mrs. Rhoda Lopez of one of the larger polyps as visualized through the gastroscope.

significant abdominal complaints, should suggest polyposis of the intestinal tract as a source of blood loss.

4. Although this syndrome has been reported with increasing frequency during the past few years, there is evidence that it is nevertheless a very rare entity. A survey for the purpose of detecting cases of intestinal polyposis throughout the State of Michigan had not, prior to the reporting of this case, revealed one case of polyposis associated with melanin pigmentation of the type described by Jeghers.

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MASSIVE LIPOID GRANULOMA OF THE LUNG AND ITS TREATMENT*

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SINCE Laughlen's[1] first report in 1925 of lipoid pneumonia in the human, many reports of this condition have appeared in the literature.[2] The oil (animal, vegetable or mineral) enters the lung either through direct instillation or indirectly through some defect in the swallowing mechanism, e.g., cardiospasm, neurogenic diseases, debilitated states.[3] The pulmonary pathology depends on the

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type and amount of oil that has entered the lung.[4] The acuteness of the lesion is dependent on the physical-chemical properties of the aspirated oil. The more inert the oil, the less acute the reaction. The lesions vary from interstitial pneumonitis to granulomatous lesions simulating malignancy. The location of the aspiration sites in order of frequency are right upper lobe, right lower lobe, right middle lobe, and left upper lobe. Clinically the patient may be asymptomatic, or he can present the entire gamut of respiratory symptomatology. Roentgenographically the findings may take the form of slight increase of bronchovascular markings, small scattered areas of consolidation or large confluent densities simulating malignancy. It can therefore readily be seen that those patients who have a swallowing difficulty and whose clinical and radiographic findings suggest primary pulmonary malignancy present a formidable problem as to diagnosis and therapy. The differential diagnosis may even be difficult at the time of exploration. The following case serves as an example of such a problem.

Case Report

A 64 year old white male has been seen by one of us (S. S.) since 1948 because of mild difficulty in swallowing. An esophagram taken May 28, 1948, revealed a cardiospasm with moderate dilatation of the esophagus above the cardia. Since July, 1952, the patient has had repeated episodes of coughing and wheezing, with production of a small amount of yellowish sputum. Repeated chest x-rays showed a large, wedge-shaped atelectatic area in the right middle lung field (figure 1) which has remained stationary in size. He was admitted to the Rochester General Hospital on November 9, 1952, for further studies.

Fig. 1. Postero-anterior and lateral chest x-ray showing large wedge-shaped mass involving upper and middle lung fields on right side.

Physical examination revealed a well developed, well nourished man in no acute distress who presented no significant pulmonary or other findings.

Laboratory Data: Red blood cells, 5,260,000; hemoglobin, 16.2 gm.; color index, 1.07; white blood cells, 8,500; segments, 71; lymphocytes, 27; monocytes, 2. Urine:

FIG. 2. Large, partly necrotic lipogranuloma of upper and middle lobe of right lung, with small scattered areas of lower lobe.

specific gravity, 1.025; albumin and sugar, negative; microscopic, negative. Nonprotein nitrogen, 39; sugar, 91; Old Tuberculin 1:100 negative.

Bronchoscopy performed on November 11, 1952, showed normal findings. Bronchial secretions taken at this time showed many pus cells, superficial bronchial epithelial cells and no malignant cells. Culture showed a few pneumococci and *Monilia albicans*. No acid-fast bacilli were found on direct smear or on concentration.

Exploratory thoracotomy on the right side on November 19, 1952 (G.R.B.), revealed a large mass involving the lower portion of the upper lobe and the entire middle lobe reaching almost to the hilus. Several small nodules were palpable in the lower lobe. The pleural cavity was free, and the hilar lymph nodes were soft and anthracotic. Since the mass grossly appeared to be malignant, to both the surgeon and the pathologist present at the operating table, pneumonectomy was performed. After a stormy course the patient was discharged on December 26, 1952.

Pathologic Report: The right lung weighed 730 gm. The upper and middle lobe were completely fused. At or above the point of fusion a very large hard mass about 9 cm. in diameter was palpable (figure 2). The overlying pleura was smooth. The mass within the upper lobe extended to within 1 cm. of the hilus. There were a few small lymph nodes at the hilus. Scattered through the lower lobe there were less well defined areas of induration which were light in color. Microscopically the lesion showed two distinct patterns. One was a more diffuse lesion consisting of interalveolar and intra-alveolar accumulation of large foamy oil-containing cells (figure 3). It was remarkable how many of these areas showed no inflammatory reactions at all, although in many places pneumonic processes, sometimes with microscopic abscess formations, were visible. The other more circumscribed lesions showed large necrotic patches surrounded by granulation tissue (figure 4). The granulation tissue showed many giant cells, some of which showed oil vacuoles. It is of interest to note that around the areas of necrosis the arteries showed an obliterating arteritis. This was manifested by round cell infiltration of all layers and, in addition, a marked intimal proliferation leading to obstruction of the lumina. This vascular process may have been responsible for the areas of tissue necrosis. One could see occasional peribronchial lymph nodes showing granulomatous lesions with oil vacuoles contained within giant cells. An occasional bronchus showed intraluminar plant cells surrounded by leukocytes.

Diagnosis: Oil granuloma of the right lung.

Chemical Report: The tumor-like material which was oily was removed from the lung. From 37.5 gm. of this material, 8.2 gm. of oil were extracted, making a percentage of 22. The oily material was orange in color, and insoluble in alcohol but soluble in ether. The iodine value was 7.8. The saponification number was 27. No halogens were present. No sulfur was present. Phosphorus and nitrogen were present. A small amount of cholesterol-like substance was detected. From these data the following conclusions can be drawn:

The material is not a radiopaque, oil-containing halogen; it is an oil with which some tissue oil has been extracted, which would account for the presence of phosphorus, cholesterol-like substances, a low iodine value and saponification number. The material is most probably extrinsic in origin, due to the low iodine value and saponification number, and is a saturated paraffin-like substance rather than a naturally occurring oil.

The patient gave no history of oil ingestion. After the laboratory reports were obtained we questioned him again about having taken oil in any form; however, a negative answer was repeatedly obtained. On review of the office records of one of us (S. S.) it was found that mineral oil had been ordered five years previously.

This brings out the point of how difficult it may be to get positive histories for oil intake, especially if one considers the fact that many foods may contain mineral oil in hidden form.

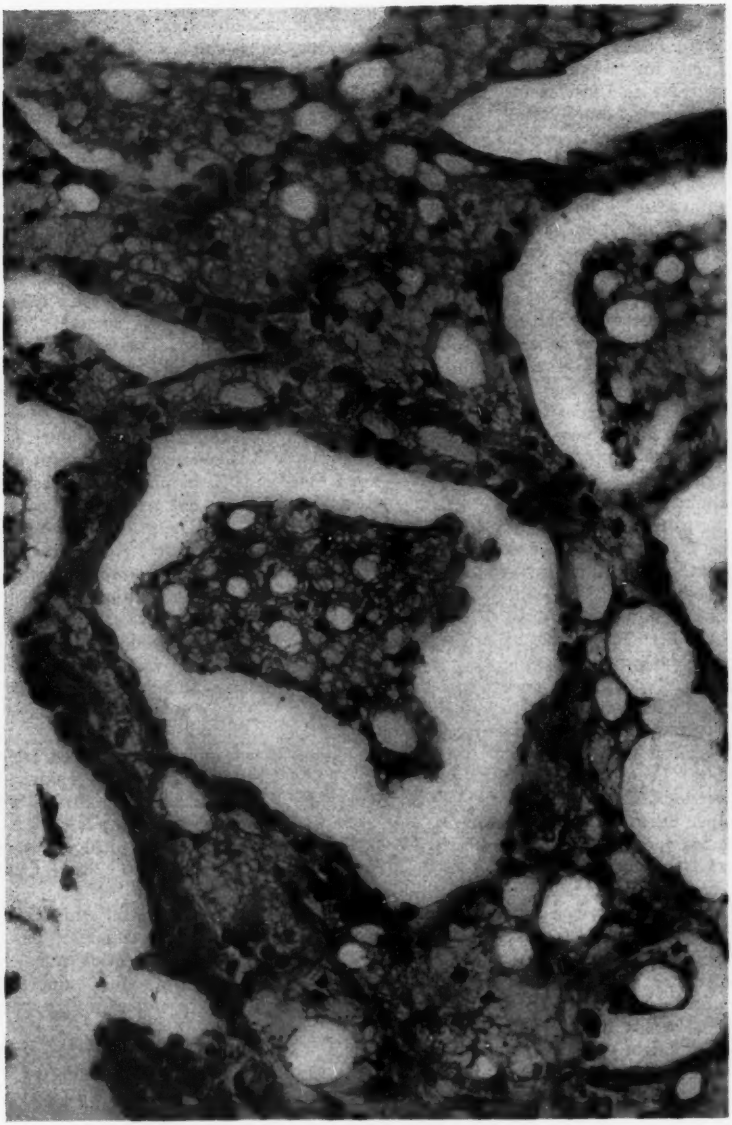

FIG. 3. Intra-alveolar and inter-alveolar infiltration of lung with oil-containing cells.

FIG. 3. Intra-alveolar and inter-alveolar infiltration of lung with oil-containing cells.

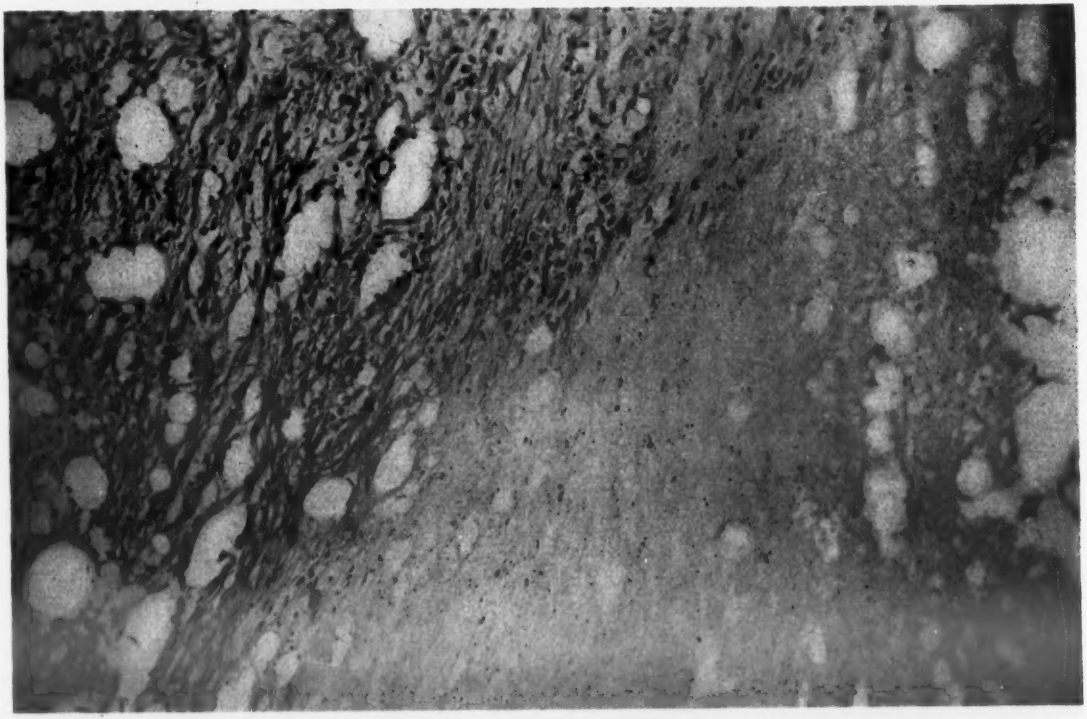

FIG. 4. Area of necrosis and granulation.

Discussion

The problem presented here was the differential diagnosis of a unilateral pulmonary mass in a case of cardiospasm of four years' duration. Attempts to establish the nature of the mass by the usual methods of examination (bronchial washings, sputa, etc.) failed to reveal anything of significance. It was therefore felt that an exploratory thoracotomy was indicated to establish a definite diagnosis.

Upon exposure, the lesion gave the impression of a malignancy to both the surgeon and the attending pathologist. Because of the extent of the lesion, pneumonectomy was performed. A frozen section was not done in this case because the lesion appeared obviously malignant. Although the value of a frozen section in establishing a diagnosis is well known, in cases of this type it may be misleading. Berg and Berford [4] presented a case where the frozen section gave a positive diagnosis of cancer, in a lesion which on permanent section proved to be a lipoid granuloma. On the other hand, Wood [6] presented a case of lipoid pneumonia associated with alveolar carcinoma of the lung. It can therefore readily be seen that one may obtain a negative frozen section in the periphery of of the lesion that may bear malignant tissue in the deeper areas of the mass.

Lipoid granulomas involving so large an area present certain dangers to the patient. The area of necrosis in the granulomas may lead to abscess formation and cavitation, with its well known serious consequences. In addition, there is a possibility that the carcinogenic properties of these paraffin-like substances may lead to the development of lung cancer at some future date, or that the concentration of normal body steroids in the oil may result in carcinogenesis. Wood [6] stressed this point in his case. Shimkin [7] has produced pulmonary cancer in mice by intratracheal injections of hydrocarbons. Twort and Lyth [8] found that several fractions of mineral oil produced primary lung tumor in mice. We therefore feel that lipoid granulomas, when feasible, should be resected. The extent of the resection should depend on the amount of lung tissue involved.

Summary

A case of massive lipoid granuloma of the lung is discussed and reasons for its surgical management are presented.

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WATERHOUSE–FRIDERICHSEN SYNDROME: REPORT OF A CASE WITH RECOVERY *

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THE sudden occurrence and rapid development of multiple petechiae, cyanosis and profound collapse in the course of an acute infection herald dramatically the condition known as Waterhouse-Friderichsen syndrome. One is stunned by the rapid and usually fatal progression of this clinical picture. First reported as an entity by Waterhouse in 1911, the syndrome received its present title following Friderichsen's report in 1918 of a similar case with a fulminating course. This case on autopsy showed massive bilateral hemorrhage into the adrenal glands. While many feel that the adrenal lesions are the significant pathologic features of this syndrome, the problem apparently remains unsolved. Autopsies have shown that these hemorrhages do not always occur.

The syndrome in most cases is associated with bacteremia caused by meningococci. Death commonly results within 24 hours of the onset of illness. Hemolytic staphylococci and streptococci have also been implicated. Anylan [1] reported an unusual case with severe infection of endometrial carcinoma. Massive adrenal hemorrhage with overwhelming septicemia was found at autopsy. Until 1940, when Carey [2] reported a case with recovery, the disease was considered universally fatal. Since this paper, an increasing number of survivals have been reported. Nelson and Goldstein [3] in 1951 reversed the grave outlook in Waterhouse-Friderichsen syndrome by reporting two cases who responded dramatically to cortisone.

A case with recovery was also reported by Wheeler.[4] Breen [5] reported on two cases; one, admitted in extremis, died, and the other recovered under cortisone therapy. Uhl,[6] reporting a case of Waterhouse-Friderichsen syndrome, did not feel that the peripheral vascular collapse was entirely the result of adrenal cortical insufficiency. He successfully treated his patient with norepinephrine over a period of 60 hours to combat peripheral vascular collapse. No serious impairment of adrenal cortical function during the acute stage of the illness or after recovery was found in his patient through various physiologic studies.

The present paper deals with a case of lobar pneumonia with lung abscess which was complicated by the Waterhouse-Friderichsen syndrome. Although no organisms were found on blood culture, sputum studies isolated alpha streptococci, which presumably could have been the causative agents.

CASE REPORT

A 58 year old white male was admitted on April 6, 1953, with a chief complaint of difficulty in breathing. He dated the onset of his illness to about two days prior to admission, when he had noted the onset of fever, pain in the right chest, cough and malaise. On the day before admission he continued to cough and began to bring up rusty sputum. His past history was negative for any serious illnesses. For approximately three years he had complained of epigastric discomfort, and in July,

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1952, had been admitted to the Wilmington General Hospital for the first time. Gastrointestinal x-rays at that time showed localized thickening of the mucosa of the posterior wall of the stomach, which the radiologist thought might have been due to an ulcer. In addition, there was definite evidence of a duodenal ulcer, as well as enlargement of the duodenal loop suggesting swelling of the head of the pancreas. Serum amylase at this time, however, was only 91 units. The patient was treated conservatively and improved. Until the admission here reported he had done very well.

On admission, the patient was apprehensive but appeared in good general condition. He was dyspneic but not cyanotic. His pulse was 92, with good volume; respirations, 24; blood pressure, 115/70 mm. of Hg. The temperature was 103° F. The skin was clear of eruptions and petechiae. There was no nuchal rigidity. The

FIG. 1.

chest was fixed in the inspiratory phase with increased intercostal spaces. No friction was noted. There was dullness to percussion over the right apex, with bronchial breathing in this region and many coarse râles. The heart appeared normal. The epigastrium showed slight tenderness; the abdomen otherwise was within normal limits. A diagnosis of right upper lobar pneumonia and old peptic ulcer was made.

Laboratory work on admission indicated negative serology. Blood sugar was 116 mg.%, and blood urea nitrogen was 23. Urinalysis was within normal limits. Red blood count was 5,080,000, with a hemoglobin of 15 gm. or 100%. White blood count was 5,500, with 20% juveniles, 20% stabs, 48% segmented neutrophils and 12% lymphocytes. The white cells showed toxic granulations. Sputum culture grew out alpha streptococci sensitive to all common antibiotics. No acid-fast bacilli were seen on sputum smear. Chest x-ray by portable technic on the day of admis-

sion showed a large, oval area of increased density in the right upper lung field, which could have been either pneumonic consolidation or tumor mass. Electrocardiogram on April 6, 1953, showed low voltage in the standard leads, with upright QRS complexes in I and II, diphasic QRS in Lead III. Q_3 and Q_3 were present. T_3 and T_3 were inverted. It was felt the tracing indicated an old infarction involving the posterior surface of the left ventricle.

The patient was started on Crysticillin, 300,000 units twice daily. On the day after admission his temperature had returned to normal and remained so except for elevation to 102.8° F. on April 8 until April 11. He continued to cough, to bring up rusty sputum and to complain of chest pain. On April 10, at 10:00 p.m., his condition began to deteriorate rapidly. He suddenly became increasingly dyspneic, and small petechiae were noted over both feet, particularly about the toes. His pulse became rapid and weak. Laboratory work done at this time indicated a normal red count, but a white count of 27,650, with 81% segmented neutrophils, 4% stab

FIG. 2.

cells, 14% lymphocytes and 1% monocytes. Coagulation time was 4 minutes, 45 seconds, or 71.6% of normal. Platelet count was 226,000 per cubic millimeter.

Twelve hours later, on the morning of April 11, the patient was markedly dyspneic, even in an oxygen chamber. The skin over practically the entire body showed small petechiae and larger, purplish, ecchymotic spots. These were most marked about the feet, hands and face (figures 1 and 2). There were frank hemorrhages into both conjunctivae, and hemorrhagic areas about the lips and gums. Examination of the lungs showed consolidation of the right upper lobe, with many râles, and tubular breathing over this area as before. The left lung appeared normal. Heart sounds were difficult to hear, only a faint irregular beat being audible. The pulse was barely palpable; it could not be counted. Blood pressure could not be obtained. Electrocardiographic changes were similar to those seen on April 6. It was felt at this time that the patient had adrenal failure superimposed upon a massive lobar pneumonia with overwhelming toxemia.

He was given 300 mg. of cortisone in three divided doses that day (April 11),

and 200 mg. daily for two days, 500 c.c. of whole blood, 1,000,000 units of aqueous penicillin intravenously every six hours, and continuous intravenous infusions of 5% glucose in 3,000 c.c. daily. Blood culture taken on April 11, but reported 10 days later, showed no growth. Chest x-ray by portable technic showed essentially the same findings of massive upper right lobe consolidation as five days previously. By late afternoon the patient's pulse was counted at 110 and very weak. By the next morning his blood pressure was obtained at 130/90 mm. of Hg. On April 13 electrographic findings were the same as previously. Total eosinophil count was 270 per cubic millimeter. On April 14 cortisone was reduced to 100 mg. daily.

The patient now continued to show slow but continuous improvement. No new purpuric manifestations were noted after those appearing on April 11. His penicillin dosage was changed to 500,000 units of aqueous penicillin intramuscularly four times daily on April 14, and then to 600,000 units of Crysticillin twice daily on April 17. He began to be increasingly comfortable out of oxygen. His blood pressures were consistently read at 90–100/60–70 mm. of Hg, and on April 20 cortisone was further reduced to 75 mg. daily. From April 11 to April 20 the patient persistently ran a temperature over 100° F., with almost daily spikes to 102° F. in the late afternoon. Thereafter it remained normal.

Chest x-ray on April 20 showed no diminution of the infiltration of the right upper lobe. At this time a fairly large cavity in the center of the area of consolidation was seen. In addition, multiple small cavities were apparent throughout the affected portion of the lung. He continued to have dullness over the right apex, with bronchial breath sounds and coarse râles. Bronchoscopy on April 25 showed the bronchial mucosa markedly red and thickened on the right side. A moderate amount of thick purulent secretion was aspirated from the right main bronchus. There was no evidence of granulations, neoplastic disease or other obstruction. The smears and cell block of the secretions failed to show any tumor cells or acid-fast bacilli.

During this time the patient showed steady improvement. By March 1 the purpura had completely disappeared, the folds of the palms having shown the last remaining manifestations. The patient was ambulatory and was increasing in strength and weight daily. Gastrointestinal series on April 27 showed changes in the duodenal bulb secondary to an old ulcer. The mucosa of the stomach appeared thickened as before, but the duodenal loop was entirely normal in contour. Chest x-ray on April 30 showed cavitation in the right upper lobe as before, but fluid and air could now be seen in the cavities.

On May 2 postural drainage was started, and the patient brought up approximately three cups of foul, gray, watery sputum almost daily thereafter. On culture this showed alpha streptococci and *Candida albicans*. Chest x-ray on May 5 showed further improvement, though the patient continued to have dullness over the right upper chest, with many râles and bronchial breath sounds. Total eosinophil count on May 4 was 43 per cubic millimeter. Cortisone was reduced to 50 mg. daily on May 3, then to 25 mg. daily on May 8, and was finally discontinued on May 10. The patient was discharged on May 11, ambulatory, afebrile and gaining weight. Within two months cough and expectoration had ceased. The abscess cavity had healed. Chest x-ray on May 22, was as follows: Examination of the chest in the postero-anterior and lateral projections and comparison with the last examination showed continued improvement. There was no evidence of any fluid previously seen to be loculated in one large and several small cavities. Again some slight retraction of the trachea to the right was seen, but the fibrosis of the right upper lobe and the size of the cavity remained essentially unchanged in both the antero-posterior and lateral projections as compared with the last examination. The left lung field remained entirely normal.

Discussion

The final diagnosis was massive right upper lobar pneumonia with lung abscess complicated by adrenal insufficiency. The patient presented a clinical picture typical of Waterhouse-Friderichsen syndrome. This syndrome, as described, is characterized by a prodromal phase of infection and, after a varying period, there is the sudden, dramatic onset of peripheral vascular collapse and petechial eruptions which rapidly become purpuric; necrosis and sloughing may follow. The patient is apprehensive and restless, and occasionally temporarily delirious. Mental lucidity is usually maintained. The anuria usually developed by these patients, and lasting for 24 to 36 hours after the onset of the syndrome, did not occur in this case. At no time did this output go below 200 c.c. daily, and after the second day output was maintained at levels above 1,000 c.c. Attention is called to the leukocytosis exhibited by this patient with the onset of adrenal insufficiency. Though he had been ill for several days prior to admission his total white count on admission was only 5,500. Four days later this was elevated to 27,000. The patient also showed a marked eosinophilia of 270 cells. A total eosinophil count over 50 is considered not compatible with adequate adrenal function.

This patient showed a remarkable change when started on cortisone therapy. With cortisone, massive doses of penicillin and intravenous whole blood and glucose solutions, he made an excellent recovery. Drugs such as epinephrine, commonly used to support the blood pressure, were not found necessary, nor were desoxycorticosterone acetate or aqueous adrenal cortical extract used. In addition, this patient, who had had on a previous hospital admission a proved duodenal ulcer, showed no signs of reactivation under cortisone therapy.

Summary

A case of Waterhouse-Friderichsen syndrome complicating massive lobar pneumonia and lung abscess is presented. This patient showed immediate improvement with cortisone used in addition to antibiotics and supportive therapy of whole blood and intravenous fluids.

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MINERALOCORTICOID-LIKE DISTURBANCE ASSOCIATED WITH ADRENAL METASTASES FROM A BRONCHOGENIC CARCINOMA *

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A few patients with Cushing's syndrome have severe electrolyte disturbances in the form of hypokalemia, hypochloremia, alkalosis and hyperglycemia.[1, 2] We are reporting a patient who lacked most of the features of Cushing's syndrome but in whom this type of biochemical disorder prompted an investigation of the adrenals and revealed an unusual group of findings. The urinary corticoid output was increased. Pyelography showed an adrenal tumor, but the tumor removed surgically proved to be metastatic and autopsy showed the tumor to have originated in the lung.

CASE REPORT

The patient was a 56 year old office worker who had been obese for many years. His health had been good until March 8, 1953, when he became irritable and began to tire easily. A week later the family doctor prescribed bromide and phenobarbital medication. (Careful questioning of the patient and his wife revealed that no other drugs, including alkalis, cortisone or digitalis, had been taken.) On March 16 the patient was feverish and perspiring markedly. The next day he became drowsy; relatives described his eyes as glazed and they noticed a dusky red flush to his face. During March 19 and 20 he passed about 10 or 12 soft brown stools involuntarily. This was the only time diarrhea occurred. The food and fluid intake was very small during these days of acute illness. On March 22 he was sweating, feverish and sleeping long periods, but was alert enough if roused to recognize and talk to relatives.

Three years previously the patient had had recurring attacks of biliary colic. Following removal of the gall-bladder, which contained many stones, he felt well. In April, 1952, the only abnormality on a routine physical examination was a blood pressure of 170/100 mm. Hg. At that time the patient commented that doctors had found his blood pressure elevated before but when he relaxed it had always fallen to normal. The urine was normal with regard to sugar, albumin and microscopic findings.

Physical examination on admission to the Toronto General Hospital on March 23, 1953, showed him to be obese (usual weight, 218 pounds), very drowsy and severely dehydrated. His face was flushed and cyanotic. His blood pressure was 130/70 mm. Hg. Although disoriented as to time and place he recognized his wife, a friend and the doctor.

The admission urine specimen contained 2 plus sugar and the fasting blood sugar on the following day was 388 mg. per 100 c.c. The next day, March 25, the fasting blood sugar was 325 mg. and the carbon dioxide combining power 97 vol. per 100 c.c. (checked). On March 26 the blood sugar was 375 mg., carbon dioxide combining power 114 vol., serum potassium 10 mg., chloride (as NaCl) 432, and sodium 336 mg. per 100 c.c. The blood pH was 7.7 on March 27. Figure 1 shows the biochemical state and treatment throughout the period in hospital.

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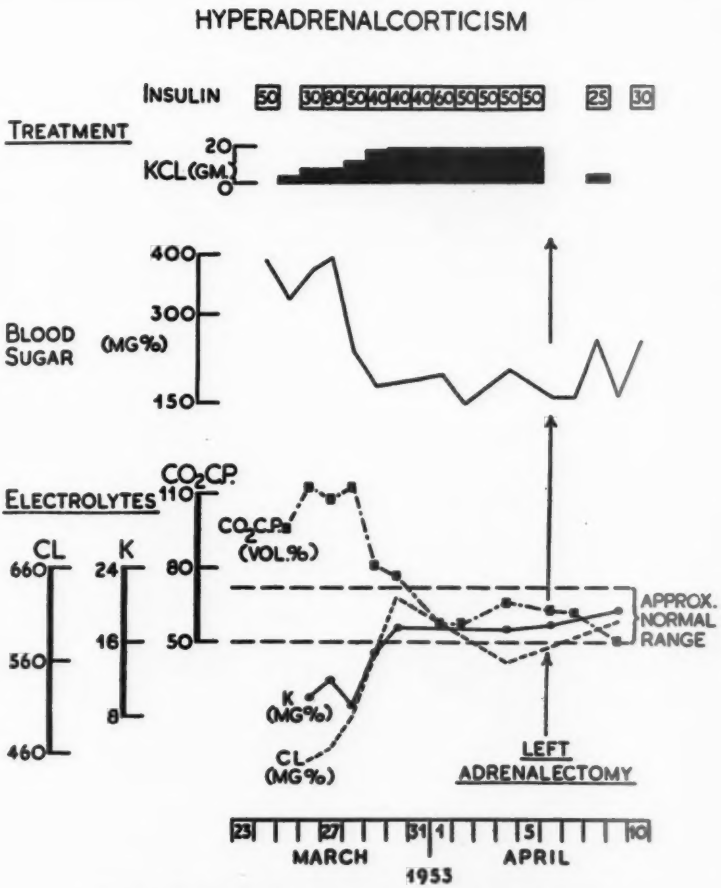

FIG. 1. The biochemical state and changes during treatment.

The patient's mental state could be correlated with the biochemical disturbance. On March 24 he said there were mice running around in his bed and trains passing by the window of his room (on the fourth floor). He referred to nonexistent pictures on the wall. It rained on March 25 and he reported firemen at the windows squirting water. He claimed to see friends in the room when none were there. His mind cleared somewhat by March 26 but although he knew the month, his family doctor's name and the fact that he had had a cholecystectomy three years previously, he could not remember events in the immediate past. From this time until April 1 he was drowsy and somewhat confused about the surroundings, visitors and the time of day. After the electrolyte upset had been corrected his mental state remained clear until a few hours before death.

The electrocardiographic changes are shown in figure 2. The marked ST depressions the day of admission were considered indicative of myocardial ischemia or

injury. These changes disappeared during the eight days in which the blood electrolyte values were being brought to normal by the administration of large amounts of fluid and potassium chloride (with ammonium chloride added for a few days).

Absolute eosinophil counts on March 27 and 29 were 11 and 44 per cubic millimeter, respectively. Urinary 17-ketosteroids were determined according to the stand-

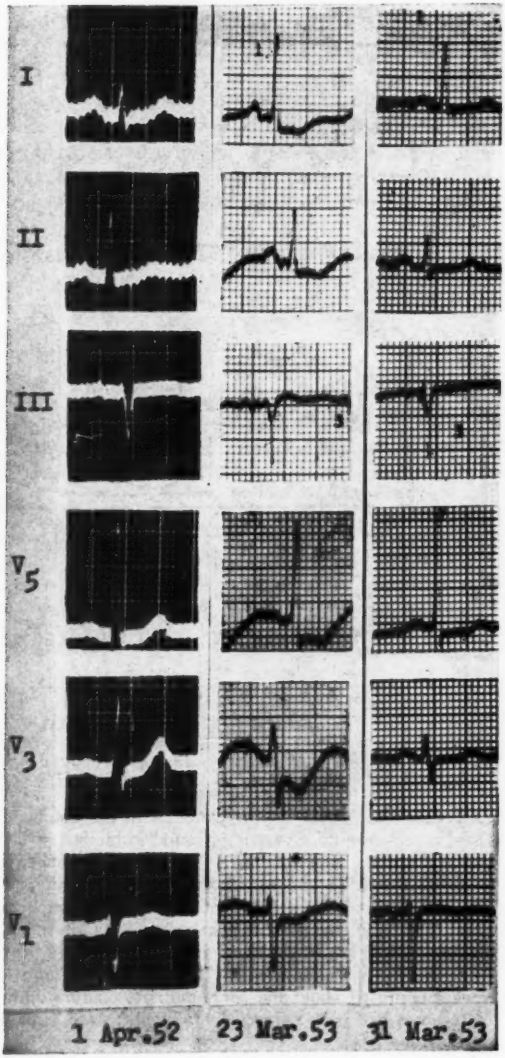

FIG. 2. Note: normal tracing a year before this illness; March 23, 1953: extreme ST depressions with lowering of T waves in leads I, II, V_1, V_5 and V_3; March 31, 1953: return to normal after potassium chloride therapy.

TABLE 1

Date	17-Ketosteroids mg. per 24 hr.	"Corticoids" mg. per 24 hr.	11-Oxysteroids* mg. per 24 hr.
March 27	11.3	8.1	4.2
March 29	16.9	8.5	4.6
March 30	21.5	11.8	6.7
April 5	24.8	13.7	6.5
April 6	35.1	12.6	7.5
April 7	46.9	13.4	7.9
April 8	41.6	13.3	—
April 9	38.5	12.7	—

* These are values obtained on the aqueous phase after benzene: water partition. The hydrazones showed a λ maximum at 470 mμ, suggesting that the free steroid in the patient's urine extract was largely hydrocortisone or cortisone.

ard procedure of the Medical Research Council, Britain [3] and corticosteroids by the method of Gornall and Macdonald.[4] The results are shown in table 1. Expected normal values in our laboratory for a man aged 56 are: 17-ketosteroids, 7–17 mg.; "corticoids," 1.5–3 mg.; 11-oxysteroids, 0.5–1.5 mg. per 24 hours.

ACTH, 25 mg. every six hours, was administered intramuscularly from April 2 to 10. Intramuscular cortisone was given from April 6 to 10: 50 mg. every six hours on April 6 and 7; 25 mg. every six hours on April 8; 12.5 mg. every six hours on April 9 and 10. ACTH and cortisone administration undoubtedly influenced some of the urinary steroid results recorded in table 1.

An intravenous pyelogram taken March 31 showed the left kidney displaced downward by a mass thought to be an adrenal tumor. Chest x-rays taken to exclude thymic carcinoma or secondary deposits from an adrenal carcinoma revealed no evidence of either condition. A small oval density, 3.5 by 1 cm., extended upward and laterally from the superior pole of the left hilum, which appeared prominent. This shadow was considered to be an area of fibrosis, probably of no clinical significance. The x-ray appearance of the skull, including the sella turcica, was normal.

It was decided that the patient probably had a left adrenal tumor which must be removed to prevent a return of the dangerous metabolic disorder. On April 6, after four days of preparation with ACTH, Dr. C. Aberhart and Dr. C. Robson removed a left adrenal tumor, 9 by 6.5 by 2.5 cm., which was firm, movable and well encapsulated. To our surprise the pathologic report was that of a metastatic, anaplastic tumor, most probably originating in the lung. Masses of deeply staining, atypical cells varying in size and shape replaced the entire medulla and much of the cortex. Sheets of malignant cells surrounded and in places invaded the walls of blood vessels. Some central areas of tumor had degenerated. Cords of malignant cells extended to the hemorrhagic capsule.

The bulk of the tumor was freed of adherent fat, cut into fine pieces and extracted according to a procedure described by Haines,[5] based on the findings of Cartland and Kuizenga.[6] The neutral hormone residue was taken up in methanol and assayed approximately 400 μg. of "cortisone equivalent." The bulk of the solution was placed on a paper chromatogram and developed in a toluene: propylene glycol system according to Burton et al.[7] Color tests showed: (1) a substance traveling with the mobility of compound F, estimated to be about 20 μg.; (2) a slower moving spot, possibly tetrahydro E or F, also about 20 μg.; (3) a fast moving substance covering an area 2 to 10 cm. behind the solvent front in a four hour chromatogram. This last seemed to account for the bulk of the extracted material, and its identity is unknown.

Postoperatively the patient did well for the first 36 hours. The heart action then became rapid and irregular, electrocardiograms showing a variable mixture of auricular flutter, auricular fibrillation and ventricular tachycardia. Digitalis, Pronestyl

and quinidine failed to produce improvement. The blood pressure gradually fell and he died on April 10, in a state of severe vasomotor collapse.

Summary of Postmortem Findings:* At the hilum of the left lung there was a firm, grayish white mass measuring 4 by 4 cm. At the point where the left main bronchus divided into branches to the upper and lower lobes the upper lobe bronchus was narrowed by tumor. A band of neoplastic tissue extended from the left hilum to the anterior border of the upper lobe, where whitish tumor tissue lay in the subpleural lymphatics. Eight centimeters below the left apex there was a firm white nodule measuring 2 by 3 cm. Cut sections of the left upper lobe revealed a solid mass surrounding the main bronchus and extending into the lung tissue for 7 cm. There were several large, firm, grayish lymph nodes in the mediastinum near the left hilum. The mass in the left upper lobe was a bronchogenic carcinoma which had almost completely destroyed the architecture of the bronchus and surrounding lung. In the bronchus only a bar of cartilage remained intact. The tumor consisted of sheets of spindle-shaped cells with scanty eosinophilic cytoplasm. Dense fibrous stroma separated the cells. The nuclei varied in shape, size and staining reaction. Many mitotic figures were present. The mediastinal lymph nodes contained carcinoma tissue of the same microscopic appearance as the primary.

The right lung was normal.

The heart weighed 435 gm. There was moderate atherosclerosis of the coronary arteries, with marked narrowing but not complete occlusion. No recent thrombus was discovered.

The liver, which weighed 3,275 gm., was studded with numerous spherical masses up to 4 cm. in diameter. These nodules had the same microscopic appearance as the tumor in the lung.

The pancreas, which weighed 110 gm., was difficult to free from adherent fat. Histologically it was normal. Dr. G. Wrenshall, of the Banting and Best Department of Medical Research, kindly assayed the content of insulin. He estimated that the gland contained 0.22 unit of insulin per gram, which is about 10 per cent of the normal insulin content.

The right adrenal weighed 18 gm. and was very soft and friable. Little lipoid was present in the cortex, which was reddish brown in color. Microscopically there was abundant medulla. Little pigment was present in the zona reticularis; the zona fasciculata was greatly thickened and much of this thickening was due to severe interstitial edema. Some of the cell columns showed severe atrophy, and isolated cells were undergoing absorption.

There was patchy thickening of the zona glomerulosa.

At the junction between cortex and medulla, invading each, there was a small nodule of secondary oat-cell carcinoma. This projected into a small radicle of the central vein but the latter was not thrombosed.

The femur was normal, with no evidence of osteoporosis.

The pituitary was not studied because permission to examine the head was denied.

Discussion

This patient, though suffering from a biochemical disturbance characteristic of adrenal cortical hyperfunction, had neither Cushing's syndrome nor the adrenogenital syndrome. We found no evidence of sustained hypertension, polycythemia, muscle wasting, persistent muscle weakness, striae, purpura, loss of libido, or hirsutism, though these were sought. (It is true that in April, 1952, a single blood pressure reading was 170/100 mm. Hg, but of the 12 readings re-

* Dr. H. J. Barrie of the Department of Pathology, Banting Institute, Toronto, has kindly reviewed the pathologic material.

corded in hospital prior to the adrenalectomy the highest systolic pressure was 130 and the highest diastolic 82 mm. Hg.) The absence of the usual findings of Cushing's syndrome is puzzling. Perhaps the fulminating course of the adrenocortical overactivity had been too short to allow the changes mentioned to occur. There may be other explanations. It is well known that side reactions to therapeutic doses of cortisone and ACTH occur in a few susceptible patients. Some of these "vulnerable" individuals develop a full-blown Cushing's syndrome, whereas others show only a part of the constellation of clinical and laboratory abnormalities. There may be a marked individual variation in the pattern of steroid hormones elaborated by the adrenal cortex under the influence of ACTH, or in the response of different individuals to similar hormones. Cortisone may disturb the pattern of production of adrenocortical hormones to varying degrees in different patients. It is also possible that this patient was producing, in addition to hydrocortisone, an unusual amount of a particular adrenal hormone capable of causing profound changes in electrolyte metabolism, but little else. The unidentified mineralocorticoid of Grundy et al.[8] and Simpson et al.,[9] which occurs also in humans,[10] comes to mind, but at the time our facilities were not adequate to establish its presence. The fast moving component in the tumor extract did not possess the same mobility as the substance these authors describe.

The diagnosis of hyperadrenocorticalism rests on the following: hyperglycemia, which was not fully corrected by an average dose of about 50 units of protamine zinc insulin daily; lowered serum potassium and chloride levels; extreme elevation of the carbon dioxide combining power; urinary "corticoid" excretion of about four times the normal amount, and eosinopenia. It seems probable, from our present knowledge, that the alkalosis developed initially as a result of renal reabsorption of sodium. Such an alkalosis tends to cause a replacement of cellular potassium by sodium, as a result of which the alkalosis is aggravated and large amounts of potassium and chloride may be lost in the urine.[11] The profuse sweating might act as a contributory factor in the development of the electrolyte disturbance that occurred.

The relationship of the adrenal cortical overactivity to the occurrence of metastatic adrenal tumors is difficult to understand. The two findings may have been completely coincidental, for metastasis of bronchogenic carcinoma to the adrenals in a middle-aged man is a relatively common occurrence. A possibility that seems rather unlikely is that the presence of metastatic deposits in the adrenals may have stimulated the cortices to overproduce corticoids by some sort of irritative effect. There is also little reason to suppose that the metastases replaced enough adrenal tissue to lower cortical hormone output, thereby stimulating the anterior pituitary to produce an excess of ACTH which gave rise to hyperadrenocorticalism. Apart from pure coincidence, there remains the possibility that the adrenocortical hyperfunction exerted a carcinogenic effect which either initiated or hastened the growth of the bronchogenic carcinoma. In 1943 Thompson and Eisenhardt[12] reviewed autopsied cases of Cushing's syndrome reported in the literature; 22.4 per cent of these cases had malignant tumors, two being in the pituitary, 16 in the adrenal cortex, three in the thymus and one in the ovary. Other instances of malignant tumors associated with adrenocortical hyperfunction include: the finding of a very small bronchogenic carcinoma in a case reported by Brown in 1928,[13] as well as three additional case reports of thymic carcinoma, several examples of partial Cushing's syndrome associated

with so-called masculinovoblastomas, a malignant ovarian tumor, four reports of carcinoma of the pancreas, and one of a sympathicoblastoma associated with Cushing's syndrome, referred to in a well documented article by Plotz et al.[14] These authors analyzed the reports of 114 autopsied cases of Cushing's syndrome and found that 10 per cent had malignant tumors involving organs OTHER THAN the adrenal and pituitary glands. We were impressed by these figures until we found that 9 per cent of a series of 100 consecutive patients dying of myocardial infarction and autopsied in our pathology department had malignant tumors. Myocardial infarction was selected as a common condition with no known relationship to malignant disease.

In 1952 Thorne [15] reported two cases of Cushing's syndrome associated with bronchogenic carcinoma. He was able to find recorded in the literature 11 cases of intrathoracic tumor occurring with Cushing's syndrome. Of these 11, nine were thymic carcinomas, one either a bronchogenic or a thymic carcinoma, and another a bronchogenic carcinoma.[13] He made several points which our case further illustrates. The neoplasms of lung have been of the oat-cell type in each instance. Where malignant tumors are associated with adrenocortical hyperfunction the illness tends to be fulminating; severe metabolic disorders, with diabetes as a common feature, are more likely to occur than in adrenocortical overactivity without coincidental carcinoma.

CONCLUSIONS

This case demonstrates that diabetes and severe alkalosis may occur as the outstanding evidence of adrenocortical overactivity in the absence of most of the features of Cushing's syndrome. Profound mental disorder and changes in the electrocardiogram disappeared when the alterations in hydration, potassium, chloride and carbon dioxide combining power were corrected.

The occurrence of bilateral adrenal metastases from a bronchogenic carcinoma raises the question of the relationship of the malignant disease to the adrenocortical overactivity. The two conditions may have been coincidental, the metastases may have been responsible for the altered adrenal function, or the tumor growth may have been influenced by a possible carcinogenic action of certain adrenal steroids.

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RELAPSING FEBRILE NODULAR NONSUPPURATIVE PANNICULITIS (WEBER-CHRISTIAN SYNDROME): CASE REPORT WITH RESPONSE TO ROENTGEN THERAPY, AND FAILURE OF CORTISONE*

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Relapsing febrile nodular non-suppurative panniculitis is an uncommon disease of unknown etiology. In a review article Beerman [1] found 83 reported cases. No review of the literature is here included, as this has been done recently.[2, 3] Our case is reported because it showed that, although cortisone apparently caused the disappearance of fever, it did not prevent the appearance of new lesions. Furthermore, one area was selected for radiation therapy and this area healed while surrounding areas did not. Then all available areas were treated by x-ray, with prompt disappearance of the lesions, disappearance of fever, and a return of blood count to normal. No relapses had occurred in the ensuing 18 months.

CASE REPORT

A 22 year old housewife was admitted to the hospital on May 25, 1953, because of fever and "bumps" in the skin of seven months' duration. She had noted the first lesion accidentally while dressing. Located in the right upper abdominal quadrant, it was firm, painless and nontender, and there were no associated general symptoms. This lesion slowly progressed in size over the next six months. About two months prior to admission she consulted a physician who told her she had a "strep throat," and she was given penicillin by injection and orally for seven days. She apparently

* Received for publication March 29, 1954.

recovered and was without symptoms until one month before admission, when she again consulted a physician because of fever.

She was given Aureomycin for three days. She believed that the temperature disappeared while taking the drug, but returned when it was stopped. Soon thereafter, new skin lesions began to appear on the right forearm, right shoulder, left forearm and left shoulder, and finally in the cheeks on May 23. During this month she experienced intermittent chills and fever and slight malaise, and vomited a bitter material with a "chlorine" taste about twice weekly. However, at no time had she taken medication containing bromine or iodine. There was no history of trauma in relation to the appearance of lesions.

A review of the systems revealed nothing of note, and the past history revealed only the usual childhood diseases. The father had had diabetes and heart disease for many years and the mother had asthma. There were three older brothers, all in good health.

Physical examination revealed a temperature of 103° F. in a patient who did not appear acutely ill. There were no remarkable findings except for the skin lesions. They were elevated, firm, nontender, irregular in shape, in the subcutaneous region. The distribution of lesions was as follows: abdomen, 8 by 8 cm.; right deltoid, 6 by 7 cm.; left deltoid, five separate lesions in an area 6 by 14 cm.; right forearm, seven lesions, each 1 to 2 cm. in diameter; and left forearm, seven lesions 1 to 3 cm. in diameter. There were no definite lesions on the face. There was a slate gray discoloration of the overlying skin.

Laboratory studies showed a white blood count of 1,900, but on the stained smear there was a slight increase in polymorphonuclears, with no abnormal cells present. The hemoglobin was 10 gm. on several determinations. The bone marrow showed

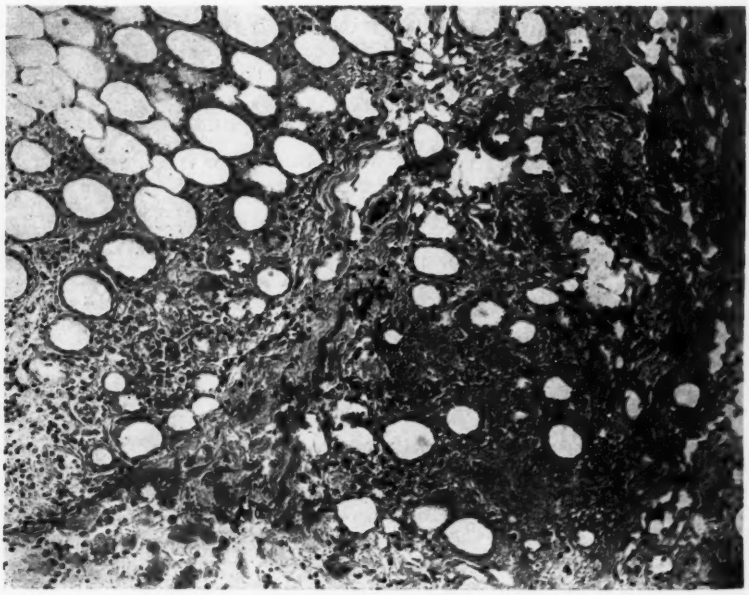

FIG. 1. Low power view of biopsy.

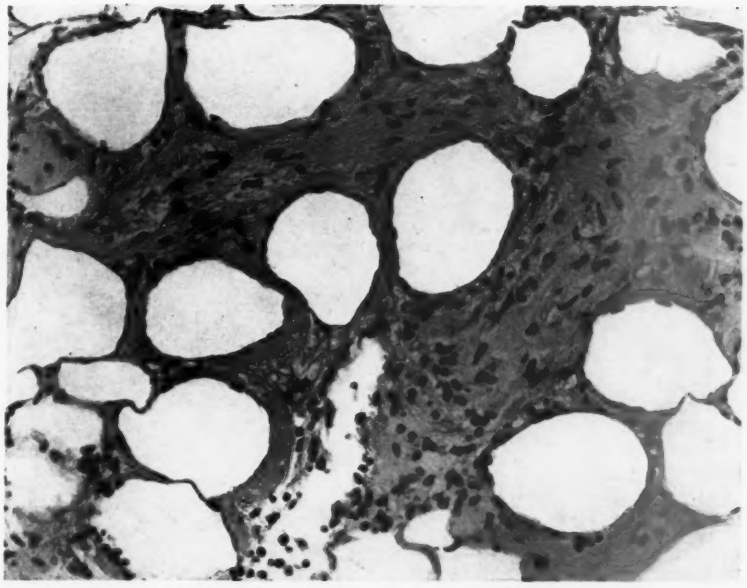

FIG. 2. High power of same specimen.

slight erythroid hyperplasia. The cardiolipin test was negative and blood sugar was 100 mg. Serum albumin was 3.1 gm., and globulin 1.6 gm. The voided urine specimens were negative for albumin and sugar; specific gravity was 1.017. On one occasion the urine contained clumps of white blood cells and on another, a few red blood cells. Urea clearance was 115 per cent of average normal. Serum bilirubin, cephalin flocculation, thymol turbidity, prothrombin time, bleeding and clotting times were all normal. One blood culture was negative. X-rays of chest, skull, pelvis and ribs showed no abnormalities. On May 28 a biopsy of the lesion of the right upper quadrant was performed. Grossly this showed only partially degenerated fatty tissue. A clinical diagnosis of Weber-Christian syndrome was made. The pathologic report was fat necrosis in the subcutaneous tissue. Microscopic examination: "Within the fatty tissue there is an inflammatory reaction characterized by infiltrations of the septa by lymphocytes, plasma cells, and large macrophages containing multiple vacuoles within their cytoplasm. In many areas, the fat cells have a border of amorphous, pink staining material without evidence of any inflammatory reaction. The vascular structure within the fat shows the inflammatory reaction in the surrounding septa, but no inflammatory involvement of the wall of the vessel" (figures 1 and 2).

During the first two weeks of observation there were irregular chills and fever, with temperature ranging from 96° F. to 104.6° F. and following no pattern. Intermittent administration of aspirin seemed to lower the temperature. The only medication given was oral and parenteral vitamin preparations, which did not influence the course of the disease. There was no significant change in the character of the lesions, and no new lesions appeared.

On June 9, 1953 she was started on cortisone, with initial dosage of 300 mg., followed by 200 mg. daily for the next five days and 100 mg. daily for the next eight days. From the day of the administration of cortisone the temperature never went

FIG. 3. New lesions that appeared on the back during cortisone therapy and just before radiation was begun.

over 100° F., and after three days of treatment was always below 99° F. There was an increase in well-being and improved appetite, and the patient was discharged from the hospital and followed as an outpatient. The white blood count rose from the 2,000–4,000 range to 7,500 without significant change in the differential count. How-

FIG. 4. *Left:* Face during cortisone therapy and before radiation. The swelling seemed to be secondary to nodular lesions in both cheeks. *Right:* After radiation therapy.

ever, on the fourteenth day of cortisone treatment she reported cramps in her calf muscles at night, facial and ankle edema, and a weight gain of 10 pounds in five days. The blood pressure was 140/96 mm. of Hg (previously 104/70 mm. of Hg). The urine was negative for sugar, and blood sugar was 90 mg. New lesions had appeared, one in the right deltoid region and a dozen or more new lesions on the back (figure 3). The cortisone was gradually reduced over a 10 day period and a mercurial (mercurophylline USP, 1 c.c. intramuscularly) was given, with good diuresis. New lesions appeared in both cheeks, and the face became so swollen that it was difficult for her to see and hear (figure 4, left). Irregular fever to 104° F. returned.

An area 10 cm. in diameter in the upper back was chosen for a trial dose of radiation. Before treatment, this area was almost completely filled with six areas of in-

FIG. 5. The area within the broken circle had received 600 r in the preceding seven days. The surrounding areas were untreated.

volvement. Outside the test area were lesions similar to those inside the area. Beginning on June 24, the patient received 200 r every other day for three treatments. (Factors: KV140, MA15, TSD 28 cm., filters .25 mm. Cu, 1.0 mm. Al.) The lesions in the treated area disappeared gradually over a seven day period, while the lesions outside the treated area were unchanged (figure 5). Fever, malaise and facial swelling remained. A lesion first noted on June 23 was excised on July 6. This was reported as acute suppurative inflammation of subcutaneous tissue (compatible with Weber-Christian syndrome) which showed necrosis, hemorrhage and leukocytic infiltration.

On the following day roentgen therapy was begun, and during the next 15 days the patient received 600 r delivered in air to the following fields: Over the right and left malar region, 5.5 cm.; over both anterior lateral aspects of the upper arms, 10 by 7 cm.; posteriorly over the right scapular area, 10 cm.; over the right and left mandibular area, 10 cm.; over both right and left forearms anteriorly, 10 cm. All of the treated areas showed rapid improvement, and fever disappeared two days after completion of radiation therapy. The patient felt generally well and her appetite was good (figure 4, right). Five new lesions, each about 3 cm. in diameter, appeared in untreated regions, but these disappeared spontaneously and by September 15 there were no subcutaneous nodules. The original right upper quadrant lesion (not treated) showed atrophy of the subcutaneous fat, leaving a saucer-like depression, but there was no scarring in the other areas.

When the patient last reported on December 17, 1954, there had been no recurrence of lesions and no fever. Her appetite was good, and the white blood count, differential count, hemoglobin, platelet count, sedimentation rate and hematocrit were all normal.

Comment

Shuman [8] reported a case in which cortisone caused the temperature to return to normal for five days, but fever returned when the drug was discontinued. This same case received radiation therapy with improvement, and the temperature remained normal for almost two months. However, another trial dose of x-ray therapy was without benefit. There are other reported failures with radiation. However, these case reports [4, 5] give no details of the therapy. Bailey [6] reports one case in which "roentgen rays were administered over the affected areas on two occasions with apparent beneficial effects." However, the patient died.

The case reported here showed a definite and good response to radiation. The area on the upper back selected for a trial dose of x-ray was in the center of many other lesions of the same duration. The lesions within the treated area disappeared rapidly, while the surrounding lesions remained unchanged. Furthermore, as treatment progressed the lesions disappeared in the order in which they were treated, while some yet untreated lesions were progressing. The white blood count rose to normal levels during radiation therapy. Fever did not disappear until treatment had been completed.

Summary

A case of relapsing, febrile, nodular, nonsuppurative panniculitis (Weber-Christian syndrome) is reported in which cortisone was administered. Although there was well-being and a return of temperature to normal during the administration of this drug, many new lesions appeared while the patient was still receiving it. An area was selected for roentgen therapy and the lesions in this area

disappeared while surrounding lesions were unchanged. The remaining areas were treated by radiation, with a disappearance of lesions and return of temperature to normal. The patient has been followed for 18 months and there have been no recurrences.

ACKNOWLEDGMENTS

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EDITORIAL

SOME ASPECTS OF IRON METABOLISM

THE unique importance of iron in mammalian physiology lies in its participation in intracellular respiration. Sixty to 70% of the body's iron is to be found in the respiratory pigment, hemoglobin. Although only minute amounts occur in the various cytochrome enzymes, here also the metal functions in respiratory processes. Iron exists in two states in the body, either chelated with a heme or porphyrin unit (as hemoglobin) or combined in a non-porphyrin form with a protein (table 1). In the latter group are included the storage forms of iron (ferritin, hemosiderin) and transport iron (iron-transferrin) in the circulating blood.[1]

TABLE 1

Approximate Composition of the Iron-Containing Compounds in the Human (70 Kilo Man)*

Compounds	Gm.	Fe in gm.	% of Total Fe
Iron Porphyrin (heme) Compounds			
Blood Hemoglobin	900	3.0	60–70
Muscle Hemoglobin (Myoglobin)	40	0.13	3–5
Heme Enzymes			
Cytochrome C	0.8	0.004	0.1
Catalase	5.0	0.004	0.1
Cytochrome a, a_3, b	——	——	——
Peroxidase	——	——	——
Non-Iron Porphyrin Compounds			
Transferrin (Siderophilin)	10.0	0.004	0.1
Ferritin	2–4	0.4–0.8	15.0
Hemosiderin	——	——	——
Total Available Iron Stores	——	1.2–1.5	——
Total Iron		4–5	100

* From Granick.[1]

Numerous studies have revealed that the metabolism of iron occurs essentially in a closed system. Absorption and excretion are minimal. It is estimated that the average American dietary intake per 24 hours contains 15 to 20 mg. of iron of which less than 10% is absorbed through the intestinal wall.[2] Badenoch and Callender employing tracer doses of radioactive iron (Fe^{59}) found an average of 5% in the blood, 87% in the feces, and 8% unaccounted-for.[3] Peterson and Ettinger, in five normal persons, found absorption to range from 1.5 to 6.5% of an oral dose of Fe^{59}.[4] In the male, excretion is estimated to be less than 1 mg. per day, whereas in females during the childbearing period excretion averages 1.5 to 2.0 mg.

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per day. Iron turnover studies indicate utilization of approximately 27 mg. per day, three quarters of which are needed for the formation of hemoglobin by the bone marrow. About 20 mg. of this total are derived from the catabolism of red blood cells, the remainder being contributed by storage iron and a small proportion by newly absorbed iron. Studies with isotopically-labelled iron demonstrated that 70 to 100% was incorporated in newly formed red blood cells in 7 to 14 days after administration. This finding has given rise to the concept of a labile iron pool, the most recently added iron being apparently in a more readily utilizable form than previously stored iron. Variations occurring in disease will be discussed below. Braunsteiner et al.[5] injected Fe^{59} into rats and found maximal labeling of liver ferritin in 24 to 96 hours with a decline thereafter. Similar studies in guinea pigs by Theorell et al.[6] also demonstrated maximal tagging of ferritin in two days, then a drop to a plateau which persisted for about a week following which an asymptotic decline occurred.

The control of absorption of iron into the body is apparently mediated by the intestinal mucosal content of the iron-containing protein, ferritin. The precursor of this protein, i.e. its non-iron containing form, is known as apoferritin. Many tissues in the body have the ability to form ferritin. Iron itself seems to be the stimulus for ferritin formation. Granick[7] demonstrated a marked increase in crystallizable ferritin in the intestinal mucosa of the guinea pig within seven hours after iron feeding. The amount of ferritin was found to diminish over a period of two to five days. Hahn[8] demonstrated that previous iron feeding led to a "mucosal block" which hindered the subsequent absorption of radioactive iron for approximately 12 to 24 hours.

Most of the iron in food occurs in the ferric state either as ferric hydroxide or as ferric organic chelates. In an acid medium these compounds are broken down into free ferric ions or loose chelates. Although the hydrochloric acid of the gastric juice is important for this purpose it appears that a similar function can be performed by the organic acids of foodstuffs. If this were not the case iron deficiency would be expected in all instances of achlorhydria, which of course does not happen. Reducing substances in the food (ascorbic acid, SH compounds such as cysteine) change ferric to ferrous ions which are more soluble and more readily absorbed by the mucosal cells. Thus it appears that the movement of iron through the mucosal cells occurs in the ferrous form. It is hypothesized that the "mucosal block" referred to above is related to the level of ferrous iron in the cell and indirectly to the ferritin concentration.

[5] Braunsteiner, H., Gisinger, E., and Pakesch, F.: Ferritin, Transferrin, und Serumeisen, Klin. Wchnschr. 30: 394, 1952.

[6] Theorell, H., Beznak, M., Bonnichsen, R., Paul, K. G., and Åkeson, Å.: On the distribution of injected radioactive iron in guinea pigs and its rate of appearance in some hemoproteins and ferritins, Acta chem. Scandinav. 5: 445, 1951.

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[8] Hahn, P. F.: Metabolism of iron, Fed. Proc. 7: 493, 1948.

In vitro studies of ferritin demonstrated an iron content of 17 to 23% in the form of ferric hydroxide micelles or clusters. The iron of ferritin can be removed in vitro by various reducing agents, for example, sodium dithionite. It is probable that in vivo a reducing enzyme may also function to remove iron from ferritin, but this has not been experimentally demonstrated. The amount of ferrous iron leaving the cells may depend on the relative redox level of the cells which is, in turn, a function of the decrease in oxygen tension in the blood stream.

Variations in absorption occur in a variety of pathological states. Diminished absorption has been demonstrated in patients with idiopathic steatorrhea, pancreatic steatorrhea, a patient with multiple resections of the small bowel for regional enteritis, etc.[3] Intravenous administration of iron in some of these patients showed normal utilization. In iron deficiency anemia, Hahn demonstrated two to ten times as much absorption as in normals. It is interesting to note that increases in absorption were also found in pernicious anemia and hypoplastic anemia. The possibility that diminished oxygen tension affecting the mucosal cells themselves or acting indirectly through a hormonal mechanism might be responsible for this must be considered. The increased body stores of iron (hemosiderosis) found at autopsy in such cases illustrates one of the dangers of prolonged iron therapy in refractory anemias. The increase in iron absorption in hemochromatosis will be discussed further below.

Experimental observations in rats indicate that a diet deficient in phosphates increases iron absorption.[9] When a diet grossly deficient in proteins, minerals and vitamins was supplemented by large amounts of ferric citrate increased absorption and storage of iron was noted in the tissues. It has been suggested that a human analogue of this experimental situation occurs in the nutritional cytosiderosis described by Gillman and Gillman in malnourished Africans.[10] The tissue changes in these cases are virtually indistinguishable from hemochromatosis.

Ferrous iron leaving the intestine is promptly autoxidized, and in the presence of CO_2 forms a complex with a metal-binding (beta) globulin known as transferrin or siderophilin. Chemical studies indicate that only about one third of the total amount of this circulating protein is combined with iron. The serum iron level plus the unsaturated or latent iron binding capacity (LIBC) is equivalent to the total transferrin or iron-binding capacity (TIBC). This ratio is of considerable significance in an understanding of various derangements of iron metabolism. Laurell[11] believes it to be an important factor in mediating iron ion activity in different organs of the body. The normal level of serum iron is 50 to 150 micrograms per

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[10] Gillman, J., and Gillman, T.: Pathogenesis of cytosiderosis as evidenced in malnourished Africans, Gastroenterology 8: 19, 1947.

[11] Laurell, C. B.: Plasma iron and the transport of iron in the organism, Pharm. Rev. 4: 371, 1952.

100 ml. of blood while the latent iron-binding capacity (LIBC), i.e. unsaturated transferrin, is 150 to 250 micrograms per 100 ml. of blood. The level of serum iron is the result of a dynamic equilibrium. The factors which influence it are hemoglobin break down, uptake by bone marrow, removal and storage in the tissues, absorption from the gastrointestinal tract, and the rate of formation and decomposition of transferrin.

Valuable information regarding the state of erythropoiesis may be gained by the use of radioactive iron in two test procedures. The rate of disappearance of tracer doses of Fe^{59} bound to plasma or iron-binding protein prior to intravenous injection has been studied by several groups of investigators.[12, 13] Under normal circumstances one half (T ½) of the radioactivity disappears in an exponential fashion from the circulating blood in approximately 90 minutes. In hemolytic anemias with their accompanying erythroid hyperplasia, and in polycythemia vera half of the radioactivity disappeared in 11 to 30 minutes. In aplastic anemia the disappearance rate was markedly prolonged to 250 minutes. Further information of importance is obtained by noting the reappearance time of radioactivity in newly formed red blood cells. Thus in iron deficiency anemia uptake in erythrocytes is accelerated while in aplastic anemia uptake is diminished.

Most tissues have the ability to store iron in the form of ferritin which is microscopically invisible. When tissue stores of iron are increased it becomes microscopically visible in the form of hemosiderin. Hemosiderin contains approximately 35% of iron combined with protein in a manner similar to ferritin. In man the highest concentrations of ferritin occur in the liver, spleen, and bone marrow. It has been estimated that the normal iron store is 1.2 to 1.5 gm., i.e. an amount sufficient to supply the iron of 1.5 to 2.5 liters of blood. Under normal conditions there is a relatively slow exchange of iron between the serum and the storage iron. Following an acute hemorrhage in a normal individual hypoferremia may persist for weeks, indicating slow mobilization from the depots.

Since all available data indicate a relatively slow build up of normal iron stores and very careful husbanding of these resources, cognizance of these facts should be taken in the management of iron deficiency anemias. Although the intestinal uptake in iron deficiency anemia may be two to ten times that occurring in the normal individual, it has been noted that once the anemia is corrected uptake slows down and tissue stores are only slowly reconstituted. It is essential therefore in the treatment of such anemias to continue the oral administration of iron for several months after correction of the blood picture. Optimal absorption of iron is best assured by administering it in the ferrous form with ascorbic acid or acid fruit juices

[12] Huff, R. L., Hennessey, T. G., Austin, R. E., Garcia, J. F., Roberts, B. M., and Lawrence, J. H.: Plasma and red cell iron turnover in normal subjects and in patients having various hematopoietic disorders, J. Clin. Investigation 29: 1041, 1950.

[13] Wasserman, L. R., Rashkoff, I. A., Leavitt, D., Mayer, J., and Port, S.: The rate of removal of radioactive iron from the plasma—an index of erythropoiesis, J. Clin. Investigation 31: 32, 1952.

one or two hours before meals. Satisfactory clinical evaluation of the adequacy of iron stores may be made by examining and estimating the number of hemosiderin granules in unstained bone marrow aspirates.[14]

Until recent years the administration of iron salts intravenously was not feasible because of the sharp limitation upon the amount which could be administered without causing toxic symptoms. This quantity, approximately 8 to 10 mg., represents the amount which can be bound by circulating transferrin. Since iron deficits of the order of 500 to 1,000 mg. often exist intravenous injection was impractical. The recent introduction of a colloidal form of iron, saccharated ferric oxide, has altered this picture.[15] In this form, colloidal ferric hydroxide attached to a sugar, doses of 100 to 200 mg. may be administered. Such preparations are promptly taken up by the phagocytes of the reticulo-endothelial system and then slowly released. Indications for intravenous iron are limited. They include patients unresponsive to oral iron (continued blood loss must be carefully ruled out), individuals who exhibit marked gastrointestinal intolerance to iron, and severe iron deficiency anemias late in pregnancy. Toxic reactions to intravenous saccharated ferric oxide have recently been discussed by Nissim.[16] Early reactions, he believes, are due to impurities in the sugars; late reactions to gradual precipitation of the compound especially in the capillaries of the lung.

The toxicity of excessive deposits of iron in the tissues is still a moot question. Toxic reactions, and even fatality, have followed the accidental ingestion of massive amounts of ferrous sulfate by children. A recent experimental study in rabbits disclosed, among other findings, periportal necrosis of the liver.[17] Slower accumulation of excess iron occurs in hemochromatosis and in so-called "exogenous" hemochromatosis or hemosiderosis. The former is believed to be basically due to a congenital defect in the mucosal absorptive regulatory mechanism. Peterson and Ettinger[4] found 20 to 45% absorption of an oral dose of radioactive iron in two patients with hemochromatosis in contrast to a normal value of 1.5 to 6.5%. Whether the cirrhosis of the liver and pancreatic fibrosis regularly seen in advanced cases are due to the excessive deposits of iron (40 to 50 gm.) or to associated pathology is not definitely known. The distribution of iron in "exogenous" hemochromatosis is essentially the same as in endogenous hemochromatosis. Many of the former cases also reveal chronic liver damage, but this may have been the result of the basic disease for which transfusions or large doses of iron were being given. Recent reports indicate that clinical improvement and depletion of the excessive iron stores

[14] Rath, C. E., and Finch, C. A.: Sternal marrow hemosiderin. A method for the determination of available iron stores in man, J. Lab. and Clin. Med. 33: 81, 1948.

[15] Nissim, J. A.: Iron toxicity, intravenous administration of iron, Lancet 2: 49, 1947.

[16] Nissim, J. A.: Toxic reactions after intravenous saccharated iron oxide in man, Brit. M. J. 1: 352, 1954.

[17] Luongo, M. A., and Bjornson, S. S.: The liver in ferrous sulfate poisoning. A report of three fatal cases in children and an experimental study, N. England J. Med. 251: 995, 1954.

may result from repeated phlebotomies.[18, 19] Long term studies of a number of cases will obviously be necessary to evaluate this method of treatment.

The physician of today is obviously better prepared than his colleague of Sydenham's era who used iron or steel filings steeped in cold Rhenish wine for the treatment of chlorosis. The uncritical continued use of multipurpose ("shot-gun") hematinics for iron deficiency anemia seems at times somewhat irrational in view of the extensive data available concerning iron metabolism.

MILTON S. SACKS, M.D.

[18] Warthin, T. A., Peterson, E. W., and Barr, J. H., Jr.: The treatment of idiopathic hemochromatosis by repeated phlebotomy, Ann. Int. Med. 38: 1066, 1953.

[19] Davis, W. D., Jr., and Arrowsmith, W. R.: The treatment of hemochromatosis by massive venesection, Ann. Int. Med. 39: 723, 1953.

REVIEWS

Diseases of the Chest. By T. Royle Dawber, A.B., M.D., F.A.C.P., and Lloyd E. Hawes, A.B., M.D., D.A.B.R., 440 pages; 18 × 26 cm. The Williams and Wilkins C., Baltimore, Md. 1952. Price, $10.00.

The introduction to this text states that "it should not be difficult for the practicing physician to achieve sufficient competence in both the clinical aspects and radiology of diseases of the chest, so as to enable him to care for almost all patients with chest conditions." Further the cover piece by the publishers emphasizes the need for such a "complete authoritative, yet simple guide to diseases of the chest and the uses of x-ray," to assist the general practitioner in his diagnosis and treatment of chest diseases. In the opinion of the reviewer it is not feasible to expect the general physician to be equipped to diagnose and treat more than a modest proportion of the subacute and chronic pulmonary diseases.

The book covers in a sketchy manner most of the pulmonary and cardiac conditions, but it is entirely too brief in its dealings with some of these. Special criticism may be pointed out, i.e., the section on sarcoid and on occupational diseases of the lungs is entirely too brief to be adequate. The chapters on tuberculosis, especially therapy, are already outmoded. For example, the section on pneumothorax, which is rarely employed, is inaccurate as to its indications, if indeed any exist at all. Pulmonary resection is spoken of lightly, yet it is being used widely at present in the arrest of tuberculosis. Streptomycin therapy is inadequately covered and there is no mention of the use of INH. In this respect, however, the authors cannot be criticized too greatly since the book was published in 1952 and is now being reviewed in 1954. During these past two years many changes have taken place in the chemotherapy of tuberculosis.

The bibliography for the most part is based on articles going back as far as 1937 to 1941. The bibliography on tuberculosis shows no reference later than 1950. Of course, any chest specialist knows only too well the changing picture in the treatment of this disease.

H. V. L.

The Chest, A Handbook of Roentgen Diagnosis. 2nd Ed. By Leo G. Rigler, M.D., Professor and Chief, Department of Radiology, University of Minnesota. 380 pages; 14 × 21 cm. The Year Book Publishers, Inc., Chicago. 1954. Price, $8.00.

The Chest is one of the series of *Handbooks of Roentgen Diagnosis.* The book is really an atlas with approximately 50 per cent of its contents being illustrations. The text is kept to a minimum with most of the descriptive material contained in the legends accompanying each illustration. This minimum reading material contains the basic roentgen diagnostic points of each disease.

Throughout the book, the emphasis is on the diagnostic criteria as manifested on routine roentgenograms of the chest. However, bronchography and body section radiography are stressed to bring out certain points and details. The important roentgen manifestations of all chest diseases are well illustrated.

The roentgenographic reproductions are excellent with the important roentgen changes being well labelled. The legends are brief and complete. In this second edition many new illustrations have been added and many of those in the first edition replaced.

The author has performed an excellent task in covering chest roentgenography so completely with so many good illustrations and a minimum amount of reading material.

J. M. D.

Verhandlungen der deutschen Gesellschaft für Kreislaufforschung. Herausgegeben von Prof. Dr. Rudolf Thauer. 334 pages; 15.5 × 23 pages (paper-bound). Steinkopff, Darmstadt. 1952. Price, Kart. DM 40.–.

The scientific papers and discussions of the 18th meeting of the German Society for Circulatory Diseases makes for interesting reading. The electrocardiogram was its main topic. Several papers discussed the present status of electrophysiological concepts of the electrocardiogram. Although the vector concept seems to prevail, an occasional argument was heard to allow survival of the differential theory. The presentations are clear, informative and well founded. Presentations on extrasystoles, left ventricular cavity potentials and vectorcardiography follow. The clinical diagnostic value of the electrocardiogram is discussed in detail by Holzmann. Numerous papers cover the various theoretical and specific clinical aspects in an informative and stimulating way. Gradient determination and vector analysis have been widely called upon to support points of argument. The remainder of the meeting included several interesting discussions on the anatomy and physiology of the arteriolo-venular anastomoses, a much neglected topic in many parts of the world.

The collection of papers on electrocardiography and other topics of cardiological interest is to be recommended to the cardiologist for the numerous facets of discussion.

A. G.

Psychosomatic Case Book. By Roy R. Grinker, M.D., and Fred P. Robbins, M.D. 346 pages; 16 × 24 cm. The Blakiston Company, New York. 1954. Price, $6.50.

This book consists of an introduction embracing the current concept of psychosomatic medicine and a compilation of 70 case histories. The range of the cases presented is somewhat wider than the usual concept of psychosomatic illness but emphasizes the psycho-physiological development and unit.

The book gives a short and concise historical survey of theoretical concepts in psychosomatic medicine. The authors are critical of most of the current theories but more in the sense that they are incomplete rather than incorrect. They attempt to formulate a broader concept considering the multi-determined factors of illnesses and oppose the concept of specificity of personality type for psychosomatic symptoms. In their thoughtfully worked out case histories the authors demonstrate the validity of their ideas by showing the many determinants in the patient's life that might have contributed to his illness.

This is an excellent book for anyone who wishes to make an intensive study in this field. But to benefit from it a certain amount of knowledge of psychoanalytic concepts is necessary. It is a useful reference book for the psychiatrist and the physician who is interested in studying more deeply the complicated problems of this field.

H. W. N.

Textbook of Pediatrics. 6th Ed. Edited by Waldo E. Nelson, M.D. 1581 pages; 18 × 26 cm. W. B. Saunders Co., Philadelphia. 1954. Price, $15.00.

This popular textbook has been extensively revised and brought up to date without increase of size. Many sections include references as late as 1953. Excellent

illustrations have been added or put in place of older ones. Those on bone age and retrolental fibroplasia are particularly noteworthy. In connection with this disease, the modern practice of avoidance of excessive oxygen administration and the necessity of prescription of oxygen in percentage rather than rate of flow are to be noted. The section on diabetes is very practical and moderate. It includes use of mixed NPH-regular insulins and recommends mild control of diet rather than so-called "free diet." Kwashiorkor is described as the "most prevalent and serious nutritional disturbance in the world today."

The practice in the text of presenting dosages in mixed systems of metric doses per avoirdupois body weight is defended on basis of current practice. The question may be raised as to whether such a textbook should not precede current usage and lead the way out of the present confusion of systems toward the complete use of the metric.

The text is remarkably free of errors of typography and material. The excessive atropine dosages on page 183 slipped by, however.

G. E. G.

Cancer: Diagnosis, Treatment and Prognosis. 2nd Ed. By LAUREN V. ACKERMAN, M.D., and JUAN A. DEL REGATO, M.D. 1201 pages; 17.5 × 25.5 cm. C. V. Mosby Co., St. Louis. 1954. Price, $22.50.

This book represents a complete revision of the authors' first book published in 1947. The purpose of this textbook is to serve as a guide in the diagnosis, treatment and prognosis of neoplastic disease. The authors have tried to integrate views on the present cancer problem. The book is rather comprehensive and serves as an excellent reference book for the present day physician.

The book is divided into two parts. The first part describes in detail subject matter of general interest in the field of malignancy. An excellent chapter is written on cancer research, which describes the histologic approach, carcinogenic agents and their action. A chapter devoted to the pathology of cancer lists many important factors between benignity and malignancy. The indications and contraindications to surgery, including preoperative care of patients, is described in brief. The present day concept of radiotherapy in the treatment of neoplastic disease is well written and offers much to the reader who is interested in radiotherapy. Each chapter has a rather extensive bibliography.

Part II of the book is divided according to systems of the body. Each chapter is divided into anatomy, incidence and etiology, pathology, clinical evolution, diagnosis, present-day treatment and prognosis. This part of the book covers practically all systems of the body; such as cancer of the skin, tumors of the mediastinum, cancer of the gastrointestinal tract and genito-urinary tract. Carcinoma of the male and female genital organs is also covered. Malignant tumors of bone and soft tissues are stressed. Studded throughout each chapter are numerous photographs of gross specimens, photomicrographs and excellent drawings that help one understand the cancer problem.

The authors have stressed clinical evolution of cancer in the hope that it will facilitate earlier diagnosis. The current treatment of lesions is stressed in each chapter. Under the heading of pathology attention has been given to gross pathology because of its importance to the clinician.

This book has been very well written and will serve as a very good reference for those seeking views on the present day cancer problem. Because of the potential newer advances in cancer therapy many of these views that are present in this book will be changed throughout the coming years.

E. H. S., JR.

Long-term Diabetes: The Clinical Picture in Diabetes Mellitus of 15–25 Years' Duration with a Follow-up of a Regional Series of Cases. By KNUD LUNDBAEK, M.D., Copenhagen, Lecturer in Internal Medicine, Aarhus University Medical School; Ophthalmological Section in Collaboration with VIGGO A. JENSEN, M.D., Copenhagen, Professor of Ophthalmology, Aarhus University Medical School. 198 pages; 17 × 25 cm. Ejnar Munksgaard, Copenhagen, and Lange, Maxwell, and Springer, Ltd., London and New York. 1953. Price, 32 Danish Croner.

His unique contribution, the author states, rests in the geographic homogeneity of his clinical population, all having been residents of Aarhus, Denmark, a city of 115,100 people. He believes he has collected data from one-fourth to one-fifth of all of the known diabetic patients in this city. Because his series covers the years 1924–1935, he is certain that he includes only those patients who could have been started on insulin had they needed it. Lundbaek studied 165 living patients of this city whose diabetes existed for 15 or more years, 108 of whom used over 40 units of insulin a day. Thirty-eight of the subjects were under 40 years old when studied. To the results of his physical examinations of them and laboratory tests, he added verified data from 69 deceased patients whose diabetes was of similar duration.

From the material so derived and from an extensive review of pertinent literature, he describes the clinical picture of "long-term" diabetes mellitus, and the "universal vascular disease" associated with it. By graphic and statistical analyses he correlates the incidence and interrelations of various physical and laboratory abnormalities to illuminate "long-term" diabetes. He discusses thus arterial hypertension and serum cholesterol, papillary necrosis of the kidney, diabetic glomerulosclerosis, renal function studies, and heart diseases. In the section on ocular manifestations stress is placed on the frequency of "diabetic pigmentopathy" of the macula lutea as well as on the occurrence of microaneurysms. The discussion of neurovascular disorders of the lower extremity reflects the confusion existing in this area because of the absence of sensitive technics to determine early vascular damage and early signs of neuropathy. Miscellaneous observations include 17-ketosteroid production, and failure of rutin and vitamin E to influence capillary fragility or retinopathy.

The author does not waver in the face of the difficulty inherent in ascertaining how closely the patient adhered to the prescribed regimen of insulin and diet. Although he too finds that many of those who followed their regimens closely nevertheless developed "complications" or "concomitants," and that some of those who disregarded advice did not appear to, he concludes with assurance that it pays to be "careful."

The author intends to follow up the 165 living patients in a similar study when their diabetes has existed for 5 and 10 more years.

This study and others already published have clarified the clinical aspects of "long-term" diabetes with its "universal vascular disease" to the extent that their existence is no longer seriously challenged. As the author implies, acceptance of the existence of the problem is a necessary prelude to its solution.

P. F.

BOOKS RECEIVED

Books received during December are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

"The Adolescent Exceptional Child, A Realistic Approach to Treatment and Training": Proceedings of the 1954 Spring Conference of the Child Research Clinic of The Woods Schools, Held in New Orleans, Louisiana, April 9 and 10, 1954, in Three Sessions. 78 pages; 23 × 15.5 cm. (paper-bound). 1954. Child Research Clinic, The Woods Schools, Langhorne, Pennsylvania. Available without

charge from Child Research Clinic, The Woods Schools, Langhorne, Pennsylvania.

Angina Pectoris: Entstehung, Erkennung, Beurteilung und Behandlung der Herzschmerzanfälle. By PROF. DR. W. H. HAUSS, mit einem Geleitwort von PROF. DR. FERDINAND HOFF. 394 pages; 24.5 × 17.5 cm. 1954. George Thieme Verlag, Stuttgart; in the U. S. A. and Canada: Intercontinental Medical Book Corporation, New York. Price, Ganzleinen DM 59.40.

Angiopathia Diabetica: Konservative Behandlung des Zuckerbrandes. By PROF. DR. M. BÜRGER. 190 pages; 28 × 20 cm. 1954. Georg Thieme Verlag, Stuttgart; in the U. S. A. and Canada: Intercontinental Medical Book Corporation, New York. Price, Ganzleinen DM 69.–

Bilharzia Snail Vector Identification and Classification (Equatorial and South Africa): Report of a Study-Group. World Health Organization Technical Report Series No. 90. 22 pages; 24 × 16 cm. (paper-bound). 1954. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 25 cents.

The Clinical Physiology of the Lungs. By CECIL K. DRINKER, M.D., D.Sc., Formerly Professor of Physiology, Harvard University, School of Public Health, Boston, Massachusetts. 84 pages; 23.5 × 15.5 cm. 1954. Charles C. Thomas, Publisher, Springfield, Illinois. Price, $5.50.

A Compilation of Paintings on the Normal and Pathologic Anatomy of the Reproductive System. Volume 2 of The Ciba Collection of Medical Illustrations. Prepared by FRANK H. NETTER, M.D.; edited by ERNST OPPENHEIMER, M.D., with a foreword by JOHN ROCK, M.D., Clinical Professor of Gynecology, Harvard Medical School. 302 pages; 32 × 24 cm. 1954. Commissioned and published by Ciba Pharmaceutical Products, Inc., Summit, New Jersey. Sold at cost—$13.00.

Diagnostic Laboratory Hematology. By GEORGE E. CARTWRIGHT, M.D., Associate Professor of Medicine, College of Medicine, University of Utah, Salt Lake City, Utah. 104 pages; 22 × 14 cm. 1954. Grune & Stratton, New York. Price, $3.00.

Emotional Problems and What You Can Do About Them: First Aid to Wiser Living. By WILLIAM B. TERHUNE, M.D., Medical Director, Silver Hill Foundation, New Canaan, Connecticut, etc. 190 pages; 21 × 14 cm. 1955. William Morrow & Company, Inc., New York. Price, $3.00.

Expert Committee on Nursing: Third Report. World Health Organization Technical Report Series No. 91. 28 pages; 24 × 16 cm. (paper-bound). 1954. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 25 cents.

The Haemolytic Anaemias, Congenital and Acquired. By J. V. DACIE, M.D. (Lond.), M.R.C.P. (Lond.), Reader in Haematology, Department of Pathology, Postgraduate Medical School of London. 525 pages; 22 × 14.5 cm. 1954. Grune & Stratton, New York. Price, $7.50.

Handbook of Medical Treatment. 4th Ed. Edited by MILTON J. CHATTON, A.B., M.D., Director of Medical Institutions, Santa Clara County, California, etc.; SHELDON MARGEN, M.A., M.D., Associate Research Biochemist, Department of Physiological Chemistry and Clinical Instructor in Medicine, University of California School of Medicine, San Francisco; and HENRY D. BRAINERD, A.B., M.D., William Watt Kerr Associate Professor of Clinical Medicine, University of Cali-

fornia School of Medicine, San Francisco, etc. 574 pages; 17.5 × 10 cm. (paper-bound). 1954. Lange Medical Publications, Los Altos, California. Price, $3.00.

Handbook of Treatment. By HAROLD THOMAS HYMAN, M.D. 511 pages; 23.5 × 15.5 cm. 1955. J. B. Lippincott Company, Philadelphia. Price, $8.00.

Healthier Living: A Text in Personal and Community Health. A Health Education Council Book. By JUSTUS J. SCHIFFERES, Ph.D., Director, Health Education Council, etc.; introduction by JOHN E. SAWHILL, M.D., University Physician, New York University, etc.; illustrations by LOUISE BUSH, Ph.D. 928 pages; 22.5 × 16 cm. 1954. John Wiley & Sons, Inc., New York. Price, $6.75.

Patologia del Estomago Operado: Segundo Congreso Argentino de Gastroenterologia, Mar del Plata, 13–18 de Abril de 1953. 482 pages; 24 × 17 cm. 1954. Editorial Universitaria, Buenos Aires.

Pediatric Diagnosis. By MORRIS GREEN, M.D., Assistant Professor of Pediatrics, Yale University School of Medicine; and JULIUS B. RICHMOND, M.D., Professor and Chairman of the Department of Pediatrics, State University of New York College of Medicine at Syracuse. 436 pages; 26 × 17 cm. 1954. W. B. Saunders Company, Philadelphia. Price, $10.00.

La Rate et ses Maladies. By GABRIEL GELIN; préface by PROFESSEUR AGRÉGÉ JEAN BERNARD. 299 pages; 25 × 16 cm. 1954. Masson & Cie, Paris. Price, 2.200 fr.

The Skin: A Clinicopathologic Treatise. By ARTHUR C. ALLEN, M.D., Associate Pathologist, Memorial Hospital, etc. 1,048 pages; 30 × 22 cm. 1954. The C. V. Mosby Company, Saint Louis. Price, $25.00.

Standard Values in Nutrition and Metabolism, Being the Second Fascicle of a Handbook of Biological Data. Prepared Under the Direction of the Committee on the Handbook of Biological Data, American Institute of Biological Sciences, the National Research Council. Edited by ERRETT C. ALBRITTON, A.B., M.D., Fry Professor of Physiology, The George Washington University. 380 pages; 28 × 21.5 cm. (paper-bound). 1954. W. B. Saunders Company, Philadelphia. Price, $6.50.

Surgery of the Caecum and Colon. By STANLEY AYLETT, M.B.E., M.B., B.S., B.Sc., F.R.C.S., Surgeon, The Westminster Hospital Teaching Group (Gordon Hospital), etc. 295 pages; 25.5 × 17 cm. 1954. The Williams & Wilkins Company, Baltimore. Price, $9.00.

Textbook of Biochemistry. 2nd Ed. By EDWARD STAUNTON WEST, Ph.D., Professor of Biochemistry, University of Oregon Medical School; and WILBERT R. TODD, Ph.D., Professor of Biochemistry, University of Oregon Medical School. 1,356 pages; 24.5 × 16 cm. 1955. The Macmillan Company, New York. Price, $12.00.

A Text-Book of Medicine for Nurses. 6th Ed. By E. NOBLE CHAMBERLAIN, M.D., M.Sc., F.R.C.P., Senior Lecturer in Medicine, University of Liverpool, etc. 492 pages; 22.5 × 14 cm. 1954. Oxford University Press, New York. Price, $7.50.

Transactions of the American College of Cardiology. Volume III, 1953. Editors: BRUNO KISCH, M.D., ROBERT P. GLOVER, M.D., and ASHTON GRAYBIEL, M.D., 259 pages; 24 × 16.5 cm. 1954. Published by The American College of Cardiology, New York. Distributed without cost to all grades of membership in American College of Cardiology; to nonmembers, $5.00 per volume.

COLLEGE NEWS NOTES

Nominations for A.C.P. Elective Offices, 1955–56

In accordance with provisions of the By-Laws of the American College of Physicians, Article I, Section 3, the following nominations for the elective offices, 1955–56, are herewith announced to the Fellows and Masters of the College:

President-Elect .....Walter L. Palmer, Chicago, Ill.
First Vice President .....Edward L. Bortz, Philadelphia, Pa.
Second Vice President ....Edward C. Reifenstein, Sr., Syracuse, N. Y.
Third Vice President .....Leland Hawkins, Los Angeles, Calif.

Regular elections will take place at the 1955 Annual Session, Philadelphia, Pa., on April 28, 1955, the date of the Annual Business Meeting, at Convention Hall, Philadelphia, General Headquarters.

The elections of nominees shall be by the Fellows and Masters. The above nominations do not preclude other nominations made from the floor at the Business Meeting.

Nominations of members of the Board of Regents and Board of Governors will be presented at the Business Meeting, as provided in the By-Laws.

Respectfully submitted,

Committee on Nominations

Wallace M. Yater, Washington, D. C., Chairman
Philip S. Hench, Rochester, Minn.
Stacy R. Mettier, San Francisco, Calif.
H. Marvin Pollard, Ann Arbor, Mich.
Eugene C. Eppinger, Boston, Mass.

Meetings, A.C.P. Committee on Credentials

The following meetings of the Committee on Credentials of the American College of Physicians have been scheduled; they will all be held in Philadelphia on the dates indicated:

March 19–20, 1955
April 23, 1955
November 11–12, 1955

Proposals of new members for action at the above meetings must be received at College Headquarters sixty days in advance of these dates. Governors may require that proposals be in their hands ninety days before the meetings.

New Life Members

It is a pleasure for the College to announce that the following Fellows have become Life Members since the publication of the January issue of this journal:

Dr. J. Gordon Barrow, Atlanta, Ga.
Dr. Harley Ernest Cluxton, Jr., Chicago, Ill.
Dr. James Garnett Willis, Fredericksburg, Va.
Dr. William Paul Thompson, Los Angeles, Calif.
Dr. Eugene H. Benson, El Centro, Calif.
Dr. Maxwell Spring, New York, N. Y.
Dr. George W. Cumbler, New York, N. Y.

The names of all Life Members are inscribed in an especially prepared volume that may be examined in the College Booth during the Annual Session.

Gifts to College Library of Publications by Members

The College is indeed grateful to the following members who have presented autographed copies of their books to the College Library of Publications by Members:

Paul Starr, M.D., F.A.C.P., Los Angeles, Calif.—*Hypothyroidism—An Essay on Modern Medicine*

Leon Schiff, M.D., F.A.C.P., Cincinnati, Ohio—*Clinical Approach to Jaundice*

Arthur Bernstein, M.D., F.A.C.P., Chicago, Ill.—*Intern's Manual (Cook County Hospital)*

A.C.P. Regional Meetings

MICHIGAN Regional Meeting, Grand Rapids, Mich., December 4, 1954; Dr. H. Marvin Pollard, F.A.C.P., Governor; Dr. Douglas Donald, F.A.C.P., Detroit, Chairman of the Program Committee; Dr. Joseph F. Whinery, F.A.C.P., Grand Rapids, Chairman of the Committee on Local Arrangements. There was an all-day scientific program at the Blodgett Memorial Hospital. This was the first time that the State Regional Meeting was held in Grand Rapids. Consensus was that the meeting was a most successful and inspiring one with an attendance larger than anticipated, 128.

NORTH CAROLINA Regional Meeting, Durham, N. C., December 9, 1954; Dr. Elbert L. Persons, F.A.C.P., Governor; Dr. Kenneth D. Weeks, F.A.C.P., Rocky Mount, Chairman of the Program Committee; Dr. E. E. Menefee, F.A.C.P., Chairman of Local Arrangements. As usual, there was a large and representative participation of the members in North Carolina—56 Fellows, 37 Associates and 50 Guests; total, 143. North Carolina is the state in which Regional Meetings were first initiated more than 25 years ago.

OHIO Regional Meeting, Cleveland, Ohio, January 14, 1955; Dr. Charles A. Doan, F.A.C.P., Columbus, Governor and General Chairman; Dr. Harold Schwartz, F.A.C.P., Cleveland, Chairman of Arrangements and Program; Dr. Boyd G. King, F.A.C.P., Cleveland, Chairman of the Banquet Committee; Dr. Marion A. Blankenhorn, F.A.C.P., First Vice President, representing the Officers and Regents; Mr. E. R. Loveland, Executive Secretary, representing the central Executive Offices. An all-day scientific program at the Veterans Administration Hospital; evening reception and banquet addressed by John Lansdale, Jr., Esq., former Chief of Security and Intelligence, Atomic Bomb Project; attendance figure not available at time of preparation of this report.

COLORADO Regional Meeting, Colorado Springs, Colo., January 14–15, 1955; Dr. C. F. Kemper, F.A.C.P., Denver, Governor and Chairman; Dr. Charley J. Smyth, F.A.C.P., Denver, Chairman of the Program Committee; Dr. William H. Beierwaltes, F.A.C.P., Ann Arbor, Guest Speaker on the Scientific Program, taking the place of President Cyrus C. Sturgis, F.A.C.P., Ann Arbor, who was absent because of illness. This was a combined meeting with the Colorado Society of Internal Medicine. Attendance figure not available at the time of preparation of this report.

PUERTO RICO Regional Meeting, San Juan, P. R., January 28–29, 1955; Dr. Raphael Rodriguez-Molina, F.A.C.P., Governor and Chairman; Dr. Ramon Suarez, A.C.P. Third Vice President, representing the Officers and Regents of the College; numerous distinguished guests. There was an all-day scientific program, concluded by a reception and dinner at the Condado Beach Hotel. The attendance figure is not available at the time of preparation of this report.

PRAIRIE Regional Meeting (Alberta-Manitoba-Saskatchewan), Regina, Sask., February 5–6, 1955; Dr. C. H. A. Walton, F.A.C.P., Winnipeg, Governor; Dr. D. E. Rodger, F.A.C.P., Regina, Local Chairman; Dr. George F. Strong, Vancouver, A.C.P. President-Elect, Special Guest. This was the first "Prairie" Regional Meeting, joining the two Provinces of Manitoba and Saskatchewan under Governor C. H. A. Walton with the Province of Alberta under the Governorship of Dr. Percy H. Sprague, Edmonton. There was a scientific program extending from the morning of February 4, Friday, through noon, February 5, Saturday, with a reception and banquet on Friday evening. President-Elect Strong not only presented a scientific paper but was the Speaker of the Day at the banquet. The attendance figure is not yet available.

DELAWARE Regional Meeting, Wilmington, Del., February 5, 1955; Dr. Lemuel C. McGee, F.A.C.P., Governor; Dr. Lewis B. Flinn, F.A.C.P., General Chairman; Dr. Ward W. Briggs, F.A.C.P., Luncheon Chairman; Dr. George H. Lathrope, Morristown, N. J., A.C.P. Second Vice President, representing the Officers and Regents; other distinguished guests include Dr. Maurice C. Pincoffs, M.A.C.P., Baltimore, Editor of the ANNALS OF INTERNAL MEDICINE, Dr. Thomas M. McMillan, F.A.C.P., Philadelphia, Governor for Eastern Pennsylvania, Dr. R. Carmichael Tilghman, F.A.C.P., Baltimore, Governor for Maryland, Dr. John Minor, F.A.C.P., Washington, Governor for the District of Columbia, and Mr. E. R. Loveland, Executive Secretary. Included in the invitation to this meeting were members and interested physicians from Eastern Pennsylvania, New Jersey, Maryland and the District of Columbia. Attendance figures not yet available.

DISTRICT OF COLUMBIA-MARYLAND Regional Meeting, Washington, D. C., February 12, 1955; Dr. John Minor, F.A.C.P., Washington, Governor for the District of Columbia and General Chairman; Dr. R. Carmichael Tilghman, F.A.C.P., Baltimore, Governor for Maryland, Co-Chairman; Dr. Richard A. Kern, F.A.C.P., Philadelphia, as Secretary General, representing Officers and Regents of the College. Details of program and attendance figure not available at time of preparation of this report.

SOUTHERN CALIFORNIA Regional Meeting, San Diego, Calif., February 12–13, 1955; Dr. Leland Hawkins, F.A.C.P., Governor; Dr. Roy A. Ouer, F.A.C.P., San Diego, Chairman of Program Committee; Dr. Samuel J. McClendon, F.A.C.P., San Diego, Chairman of Arrangements; Special Guests—Dr. George F. Strong, F.A.C.P., Vancouver, President-Elect, and Mr. E. R. Loveland, Philadelphia, Executive Secretary. After a lapse of several years, Southern California resumed its Regional Meetings in 1954, at Riverside with a large and enthusiastic participation by the members. This year the site of the meeting was moved to the Coronado Hotel, just across the bay from San Diego. The meeting takes on a social as well as a scientific aspect. The scientific program extended from Saturday morning, February 12, through Sunday noon, February 13. Pre-registration was arranged for members; a registration fee of $10.00 covered the banquet and other expenses of the meeting. A portfolio of abstracts of the papers was furnished to each registrant. At the time of the preparation of this report, the attendance figure was not yet available.

MISSOURI Regional Meeting, Columbia, Mo., February 19, 1955; Dr. Carl V. Moore, F.A.C.P., St. Louis, Governor; Dr. William A. Sodeman, F.A.C.P., Columbia, Local Chairman; Dr. Marion A. Blankenhorn, Cincinnati, A.C.P. First Vice President, representing Officers and Regents of the College and speaker at the special luncheon. This was the first Missouri Regional Meeting of the College.

Coming Regional Meetings

VIRGINIA Regional Meeting, Lynchburg, February 24, 1955.
NEBRASKA Regional Meeting, Omaha, February 26, 1955.

UTAH Regional Meeting, Salt Lake City, March 5, 1955.
KANSAS Regional Meeting, Wichita, March 18, 1955.
SOUTHERN ILLINOIS Regional Meeting, Peoria, March 19, 1955.

A.C.P. Research Fellowships—Stipends Increased

In line with one of the objects of the American College of Physicians to promote and advance clinical research, the Regents of the College first established on April 15, 1934, the "Research Fellowships of the American College of Physicians," to be awarded each year on the recommendation of the Board of Regents. These fellowships are designed especially for the benefit of young physicians who are in the early stages of preparation for a teaching and investigative career in medicine. There have previously been awarded sixty Research Fellowships, six of whom will conclude their work on June 30, 1955.

At a meeting of the Committee on Fellowships and Awards and the Board of Regents on November 13–14, 1954, six additional Research Fellowships were awarded, to start July 1, 1955, as follows:

*THOMAS T. AMATRUDA, JR., Yale University School of Medicine, for studies in the Duke University School of Medicine, Durham.

JOHN EDMUND BETHUNE, Dalhousie University Faculty of Medicine, for studies in the Peter Bent Brigham Hospital, Boston.

DAVID MORRIS KIPNIS, University of Maryland School of Medicine, for studies in the Washington University School of Medicine, St. Louis.

DAN ANDERSON MARTIN, Harvard Medical School, for studies in the University of North Carolina School of Medicine, Chapel Hill.

CALVIN ALPHEUS STANFIELD, University of Rochester School of Medicine, for studies in the University of Rochester School of Medicine, Rochester.

ALBERT I. WINEGRAD, University of Pennsylvania School of Medicine, for studies in the Hospital of the University of Pennsylvania, Philadelphia.

Stipends have been increased to the following levels, beginning July 1, 1955:

Unmarried Candidate $3,300.00
Married Candidate ..... 3,900.00, with a $300.00 increase for each child, not exceeding two (maximum, $4,500.00).

The Stengel Research Fellow, $500.00 additional to the regular stipends indicated above.

A.C.P. Traveling Scholarships and Awards

The Board of Regents on November 14, 1954, made the following Awards for 1955:

A. Blaine Brower Traveling Scholarships

Dr. Robert W. Frelick (Associate) ..... Wilmington, Del.
Dr. C. T. Hagan (Associate) ..... Wichita, Kans.

Elizabeth Archbold Bowes Traveling Scholarship

Dr. Judah L. Guravich (Associate) ..... St. John, N. B., Canada.

*Alfred Stengel Research Fellow.

Mead Johnson Postgraduate Scholarships

Dr. Albert R. Cox, Assistant Resident in Medicine, Vancouver General Hospital, Vancouver, B. C., Canada.

Dr. Allan L. Forbes, Resident in Medicine, Medical College of Virginia Hospital Division, Richmond, Va.

Dr. Donald L. Rasmussen, Resident in Medicine, University of Utah, Salt Lake City, Utah.

John Phillips Memorial Award in Internal Medicine

Dr. George W. Thorn, F.A.C.P., Boston, Mass.

1955 Directory, American College of Physicians

A new and revised Directory of the American College of Physicians will be published during the forthcoming months. The Directory will contain 1,000 or more pages. The pre-publication price to members of the College will be $6.00 postpaid. The post-publication price to members and other individuals or agencies will be $7.00 postpaid. Members who have not yet placed their pre-publication orders should do so now. It is necessary to estimate closely the number of copies required. A very small overrun, for obvious economic reasons, will be made.

The Directory will give up-to-date information concerning Board members, Committees, Constitution and By-Laws, Fellowships and Awards, Life Membership and a full geographical and alphabetical roster of members. The alphabetical roster will contain salient biographical data of all members and it is urgently requested that members promptly return their revised data forms.

Second International Congress of Allergology

The Second International Congress of Allergology will be held, by invitation of the Brazilian Allergy Society, in Rio de Janeiro, November 6–13, 1955, under the chairmanship of Dr. F. W. Wittich, Minneapolis, Minn., President of the International Association. A wide and extensive program dealing with almost all important problems of allergy and related immunology, biochemistry, pharmacology and therapeutics has been elaborated, and is under preparation by the Association and the Brazilian Allergy Society. Sir Henry H. Dale of London, Professor Pasteur Vallery-Radot of Paris, Professor Bernardo Houssay, Buenos Aires, and Dr. Robert Cooke, M.A.C.P., of New York, are to be guest speakers.

North Americans wishing to present papers should send in their requests to Dr. Fred W. Wittich, 424 LaSalle Medical Building, Minneapolis 2, Minn. All information concerning the Congress is available from the General Secretary, Dr. Bernard N. Halpern, 197, Boulevard Saint Germain, Paris VII°, France.

1955 Meeting, American Public Health Association

The Executive Board of the American Public Health Association has announced that the 83rd Annual Meeting and Meetings of Related Organizations will be held in Kansas City, Mo., Nov. 14–18, 1955. Headquarters will be the Municipal Auditorium.

Harvard University School of Public Health Announces Public Health Scholarships

Scholarships for the academic year 1955–56 will be granted to individuals of high professional promise in awards ranging from part tuition to tuition plus a stipend,

according to the qualifications and financial needs of the applicants. The scholarship funds are limited and are intended primarily for citizens of the United States.

A catalog of the school, admission and scholarship applications, and further information may be obtained by writing the Secretary, Harvard School of Public Health, 55 Shattuck St., Boston 15, Mass.

Scholarship applicants must return completed admission and scholarship applications to the Harvard School of Public Health by March 1, 1955. Scholarship awards will be announced May 1, 1955.

Postgraduate Course in Allergy

A Postgraduate Course in Allergy on the Modern Management of Allergic Diseases will be given at The Institute of Allergy of The Roosevelt Hospital, New York City, from May 9 to 20, 1955. The fee for the course is $150.00. Enrollment is limited and those desiring information should write to Robert A. Cooke, M.D., 428 W. 59th St., New York 19, New York.

1955 Examinations by Certifying Boards

The American Board of Internal Medicine, William A. Werrell, M.D., Executive Secretary-Treasurer, 1 W. Main St., Madison 3, Wis.

Written examinations to be held Oct. 17 in selected centers. Closing date for applications is May 1.

The following oral examinations have been scheduled:

Philadelphia—May 4–5	Portland, Ore.—Sept. 14–16
Washington, D. C.—May 6–7	Chicago—Nov. 30–Dec. 2

In addition, an oral examination in the sub-specialty of Gastroenterology will be held in Philadelphia, April 22–23; closing date for applications was Feb. 1. An oral examination in the sub-specialty of Cardiovascular Disease will be held in Chicago, Nov. 30, and the closing date for applications is June 1.

The American Board of Pediatrics, John McK. Mitchell, M.D., Executive Secretary, 6 Cushman Rd., Rosemont, Pa.

Oral Examinations:

New Orleans—March 4–6	New York City—June 10–12
Detroit—April 1–3	Chicago—Oct. 7–9
Washington, D. C.—Dec. 2–4	

Medical Officer Appointments in Saint Elizabeths Hospital

The U. S. Civil Service Commission has announced that applications are now being accepted for Medical Officer for filling the following trainee positions in St. Elizabeths Hospital, Washington, D. C.: rotating intern, $2,800 a year, and resident-in-training in psychiatry and in neurology, $3,400 to $4,200 a year. Appointments will be open July 1, 1955.

Applicants for the intern positions must be fourth-year students in an approved medical school. For the resident positions, applicants must be graduates from an approved medical school with the degree of Doctor of Medicine and, in addition, must have completed a full year's internship or now be serving such internship. No written test is required. The age limit of 35 years will be waived for persons entitled to veteran preference. Full details concerning the requirements are given in examination announcement No. 429(B).

Applications will be accepted until further notice by the Board of Civil Service Examiners, St. Elizabeths Hospital, Washington 20, D. C. Further information and application forms may be obtained from most post offices or from the U. S. Civil Service Commission, Washington 25, D. C.

Awards of the Association of Military Surgeons

James Somerville McLester Award

At the Honors Night Dinner of the Association of Military Surgeons of the United States, Statler Hotel, Washington, D. C., Dec. 1, 1954, the James Somerville McLester Award was presented to Miss Grace Bulman, Director, Dietetic Service, Veterans Administration and recent President of the American Dietetic Association. The award consists of a plaque and $500.00 and was established through the courtesy of the J. B. Roerig Company, Division of Chas. Pfizer & Company, Inc., by the Association of Military Surgeons of the United States.

Dr. James Somerville McLester was a distinguished Fellow of the American College of Physicians and for many years was a Regent of the College and a member of many important committees. Dr. McLester was recognized as an authority in the field of Nutrition, a field accepted today as a most important environmental factor in human health. Dr. McLester served during World War I with the rank of Lieutenant Colonel. He died at Birmingham, Ala., Feb. 8, 1954, at the age of 77.

Edward Rhodes Stitt Award

Comdr. John Ridley Seal, (MC), USN, F.A.C.P., was the first recipient of the Edward Rhodes Stitt Award for Outstanding Achievement in the Field of Antibiotic Medicine at the Honors Night Dinner of the Association of Military Surgeons of the United States.

Comdr. Seal, who is Head of the Communicable Disease Section of the Preventive Medicine Division of the Bureau of Medicine and Surgery, was cited "for the most outstanding contribution by a member of the Association in the field of antibiotic medicine during the past year." He was the recipient of a bronze plaque, a $500.00 prize, and a life membership in the Association for work he recently completed at the Naval Medical Research Unit Number 4, Great Lakes, Ill., where he was Medical Officer-in-Charge and Director of Research.

Sponsor of the Stitt Award, which is given in memory of the late Dr. Edward Rhodes Stitt, F.A.C.P., of Washington, D. C., who died in 1948, is Chas. Pfizer & Company, Inc. The award, which is to be presented annually, is given through the Awards Committee of the Association.

Sir Henry Wellcome Medal

Capt. Christopher C. Shaw, (MC), USN, F.A.C.P., was awarded the Sir Henry Wellcome Medal and Prize ($500.00) for his essay entitled "The Clinical Syndrome of Acute Renal Insufficiency." This article was scheduled for publication in the Military Surgeon, Jan., 1955. Capt. Shaw is currently The Medical Officer, Philadelphia Naval Shipyard.

J. Murray Kinsman, M.D., F.A.C.P., Dean of the School of Medicine of the University of Louisville, has been elected a Director of the Louisville Chamber of Commerce, evidencing the growing opinion that physicians should take an active part in the life of the community.

Dr. LeRoy H. Sloan, F.A.C.P., former President of the American College of Physicians, is the new Editor-in-Chief of the *Tice-Sloan Practice of Medicine*, pub-

lished by W. F. Prior Company of Hagerstown, Md. These volumes and the unique services that accompany them will be demonstrated by W. F. Prior Company representatives in Exhibit Booth No. 33 at the forthcoming Annual Session.

Dr. Sloan was recently elected President of the Institute of Medicine of Chicago, and took office at the beginning of 1955.

Others from the American College of Physicians who were elected to office are: Dr. Robert W. Keeton, F.A.C.P., Vice President; Dr. George H. Coleman, F.A.C.P., Secretary; Dr. Henry T. Ricketts, F.A.C.P., Board Chairman.

Among the newly elected officers of the American Clinical and Climatological Association are Dr. Henry M. Thomas, Jr., F.A.C.P., Baltimore, President; Drs. James M. Faulkner, F.A.C.P., Boston, and Johnson McGuire, F.A.C.P., Cincinnati, Vice Presidents; Dr. Marshall N. Fulton, F.A.C.P., Providence, College Governor for Rhode Island, Secretary-Treasurer; and Dr. W. David Strayhorn, Jr., F.A.C.P., Nashville, Tenn., Recorder.

Dr. Robert T. Porter, F.A.C.P., Greeley, has been chosen President-Elect of the Colorado State Medical Society. Drs. Kenneth D. A. Allen, F.A.C.P., Denver, and William C. Service, F.A.C.P., Colorado Springs, are, respectively, Vice President and Treasurer.

Dr. Louis N. Katz, F.A.C.P., Chicago, was elected President of the American Society for the Study of Arteriosclerosis at the recent annual meeting.

Dr. Henry B. Kirkland, F.A.C.P., New York City, has recently been elected Secretary of the Association of Life Insurance Medical Directors.

Dr. Russell M. Wilder, Sr., F.A.C.P., Rochester, Minn., received the 1954 Joseph Goldberger Award in Clinical Nutrition at a meeting of the Food and Nutrition Board of the National Research Council on Nov. 5, 1954.

Dr. John H. Skavlem, F.A.C.P., Cincinnati, was recently elected President of the National Tuberculosis Association.

Dr. Daniel L. Sexton, F.A.C.P., St. Louis, was elected Second Vice President of the Southern Medical Association at the 48th Annual Session in St. Louis in November. Dr. Milford O. Rouse, F.A.C.P., Dallas, Tex., is the newly elected Chairman of the Council.

Dr. Friedrich W. Niehaus, F.A.C.P., Omaha, Nebr., was installed as President of the Omaha Mid-West Clinical Society at the annual business meeting held Nov. 22, 1954. Dr. Donald J. Wilson, F.A.C.P., was made a member of the Executive Committee, and Drs. Robert S. Long, F.A.C.P., and Harold N. Neu, F.A.C.P., were elected Co-Chairmen of the Section on Internal Medicine.

Guest speakers and their general fields who will contribute to the program of the New Orleans Graduate Medical Assembly include Drs. Joseph B. Kirsner, F.A.C.P., Chicago (Gastroenterology); Tinsley R. Harrison, F.A.C.P., Birmingham, Ala., and William A. Sodeman, F.A.C.P., Columbia, Mo. (Internal Medicine). Conference Headquarters will be the Municipal Auditorium and the meeting will be held March 7–10.

"The Medical Educator Considers Premedical Education" was the title of an address delivered by Dr. John Z. Bowers, F.A.C.P., Salt Lake City, Dean of the University of Utah School of Medicine, at a Conference on Premedical and Predental Education that was held in Berkeley, Calif., Dec. 30, 1954, during the meeting of the American Association for the Advancement of Science. Dr. Francis R. Manlove, F.A.C.P., Denver, Director of the University of Colorado Medical Center, gave the luncheon address, "Methods of Improving Liaison and Coöperation Between the Medical and the Liberal Arts Colleges in the Western States."

Dr. Frank L. Engel (Associate), Durham, N. C., was among the principal out-of-state speakers at the annual graduate assembly, "The Dynamics of Metabolic Disease," held in Oakland, Calif., Jan. 31–Feb. 5. During the assembly, which was presented under the joint auspices of The Committee for Graduate Medical Education of the Alameda-Contra Costa Medical Association and The Institute for Metabolic Research of the Highland-Alameda County Hospital, Dr. Engel was Chairman of the session on "Acid-Base, Fluid, and Electrolyte Metabolism"; was moderator for a panel discussion on "Obesity"; discussed "Modern Concepts of Fat Metabolism," and participated in three panel discussions.

Dr. Laurance W. Kinsell, F.A.C.P., Oakland, Calif., served as Chairman of the Metabolic Clinic and as moderator for a round-table discussion of "Management of Liver Disease." Other faculty members from the San Francisco area included Drs. Leela S. Craig, F.A.C.P., Ephraim P. Engleman, F.A.C.P., Felix O. Kolb (Associate), Marcus A. Krupp (Associate), Victor M. Sborov (Associate), Donald C. Dodds (Associate), Eli R. Movitt, F.A.C.P., Joseph F. Sadusk, Jr., F.A.C.P., Jonas H. Sirota (Associate), and Stanford D. Splitter (Associate).

Dr. Monroe J. Romansky, F.A.C.P., Washington, D. C., delivered an address, "Current Trends in Antibiotic Therapy," at the Calixto Garcia University Hospital in Havana, Cuba, on Nov. 18, 1954. On Dec. 1 he presented a paper, "Use of the Newer Antibiotics," at the meeting of the Association of Military Surgeons of the United States, in Washington, D. C.

Dr. Julius H. Comroe, Jr., F.A.C.P., Philadelphia, addressed the monthly staff meeting of the University Hospital, Baltimore, Md., on Jan. 20. His topic was "The Physiological Diagnosis of Pulmonary Disease."

Dr. Harold J. Jeghers, F.A.C.P., Washington, D. C., and Dr. Lester R. Dragstedt, F.A.C.P., Chicago, recently addressed the House Officers' Association of the Boston City Hospital. On Dec. 7, 1954, Dr. Jeghers spoke on "Infectious Syndromes of the Liver and Subphrenic Space," and on Dec. 14, Dr. Dragstedt discussed "The Physiology of Gastric Secretion as Related to Peptic Ulcer."

Dr. Herman Beerman, F.A.C.P., Philadelphia, was the leader of a luncheon discussion group and also was in charge of the Exhibit and Panel Demonstration in Histopathology at the annual meeting of the American Academy of Dermatology and Syphilology, held in Chicago in December.

Under the Presidency of Dr. Alfred W. Harris, F.A.C.P., Dallas, the Texas Rheumatism Association held a scientific session, Dec. 10, 1954. Dr. Joseph J. Bunim, F.A.C.P., Bethesda, Md., Director of the National Institute of Arthritis and Metabolic Diseases, was the guest speaker.

Dr. Irving S. Wright, F.A.C.P., New York City, College Governor for Eastern New York, moderated a Heparin Symposium held Dec. 16, 1954, by the Academy of Medicine of New Jersey at Newark. Among the speakers was Dr. William T. Foley, F.A.C.P., New York City, Chief of the Vascular Clinic at the New York Hospital.

Dr. Henry L. Bockus, F.A.C.P., Philadelphia, was among the guest speakers at the annual meeting of the Puerto Rico Medical Association in San Juan, Dec. 8–12, 1954. On Jan. 26, Dr. Bockus was the guest speaker at the Sixteenth Annual Clinic Day at Mt. Carmel Mercy Hospital, Detroit.

Dr. Howard B. Sprague, F.A.C.P., Boston, on Dec. 7 spoke on "Significance of Abnormal Cardiac Sounds and Murmurs" at a joint meeting of the Academy of Medicine of Cincinnati and the Heart Council.

Drs. Thomas J. Dry, F.A.C.P., and William G. Sauer, F.A.C.P., Rochester, Minn., were among the leaders of a Seminar on Geriatric Problems, presented Dec. 6–10, 1954, at Sarasota, Fla., and sponsored by the Manasota Medical Foundation and the Sarasota and Manatee County Medical Societies.

Dr. Lowell A. Erf, F.A.C.P., Philadelphia, discussed "Hypertension and Hypotension—Etiology and Treatment" at the annual meeting of the Delaware Academy of General Practice, held in Wilmington, Dec. 10–11, 1954.

Dr. Bernard Stoll (Associate) was appointed Chief of Physical Medicine and Rehabilitation at the new Manhattan Veterans Administration Hospital, New York City, having assumed duties on December 5, 1954. Dr. Stoll formerly served in a similar capacity at the Westside Veterans Hospital in Chicago.

On Jan. 1 Drs. William D. Robinson, F.A.C.P., and William H. Beierwaltes, F.A.C.P., Ann Arbor, Mich., became, respectively, Editor and Associate Editor of the *Journal of Laboratory and Clinical Medicine*, the official publication of the Central Society for Clinical Research. They succeed, respectively, Drs. Clayton G. Loosli, F.A.C.P., and Robert H. Ebert, F.A.C.P., Chicago.

Dr. Frank M. Woolsey, Jr. (Associate), Albany, N. Y., has recently been appointed Associate Dean and Director of Postgraduate Medical Education, Albany Medical College. Dr. Woolsey is Chief of Medical Services at the Albany Veterans Administration Hospital and is also Associate Professor of Medicine at the College.

Dr. Edward J. Lynch, F.A.C.P., Shelton, Conn., retired on Dec. 1, 1954, as Superintendent and Medical Director of Laurel Heights State Tuberculosis Sanatorium. A graduate of the University of Pennsylvania School of Medicine, Dr. Lynch had been affiliated with the Sanatorium for 38 years and has been a Fellow of the American College of Physicians since 1930.

Dr. Benjamin M. Gasul, F.A.C.P., Chicago, Associate Professor of Pediatrics at the University of Illinois College of Medicine, has recently been appointed Chairman of the Department of Pediatrics at Presbyterian Hospital.

Hobart A. Reimann, M.D., F.A.C.P., Philadelphia, Pa., has accepted an appointment as Visiting Professor of Medicine to the University of Indonesia, Djakarta, Java, through the University of California, as Contract Professor of Medicine. Dr. Reimann left for Java just prior to the Holidays.

Dr. Ralph F. Schneider, F.A.C.P., New York City, has been appointed Medical Director of the Standard Oil Company of New Jersey. Assistant Medical Director since 1948, Dr. Schneider succeeds Dr. Robert Collier Page, F.A.C.P., who has become Chief Medical Consultant.

Dr. Franz H. Stewart, F.A.C.P., Miami, has recently been appointed Professor and Chairman (Pro Tem) of the Department of Medicine at the University of Miami Medical School, Coral Gables.

Under the Directorship of Dr. Edward L. Bortz, F.A.C.P., Philadelphia, and the sponsorship of the American Diabetes Association, the Third Postgraduate Course, "Diabetes and Basic Metabolic Problems," was held at The Lankenau Hospital, Philadelphia, Jan. 19–21.

Members of the American College of Physicians who were on the faculty included Drs. Frank N. Allan, F.A.C.P., Boston; George E. Anderson, F.A.C.P., Brooklyn; Joseph T. Beardwood, Jr., F.A.C.P., Edward S. Dillon, F.A.C.P., Garfield G. Duncan, F.A.C.P., W. Wallace Dyer, F.A.C.P., J. Russell Elkinton, F.A.C.P., Philadelphia; Reed Harwood (Associate), Boston; E. Perry McCullagh, F.A.C.P., Cleveland; Hugh Montgomery, F.A.C.P., Philadelphia; Henry B. Mulholland, F.A.C.P., Charlottesville, Va.; Henry F. Page, F.A.C.P., Philadelphia; Herbert Pollack, F.A.C.P., New York City; Henry T. Ricketts, F.A.C.P., Chicago; Howard F. Root, F.A.C.P., Boston; Charles R. Shuman (Associate), Philadelphia; and Priscilla White, F.A.C.P., Boston.

At the election of officers of the California Society of Internal Medicine, October 2, 1954, Dr. George K. Wever, F.A.C.P., of Stockton, California was elected Vice President. Dr. James H. Thompson, F.A.C.P., of San Francisco, was elected Secretary-Treasurer.

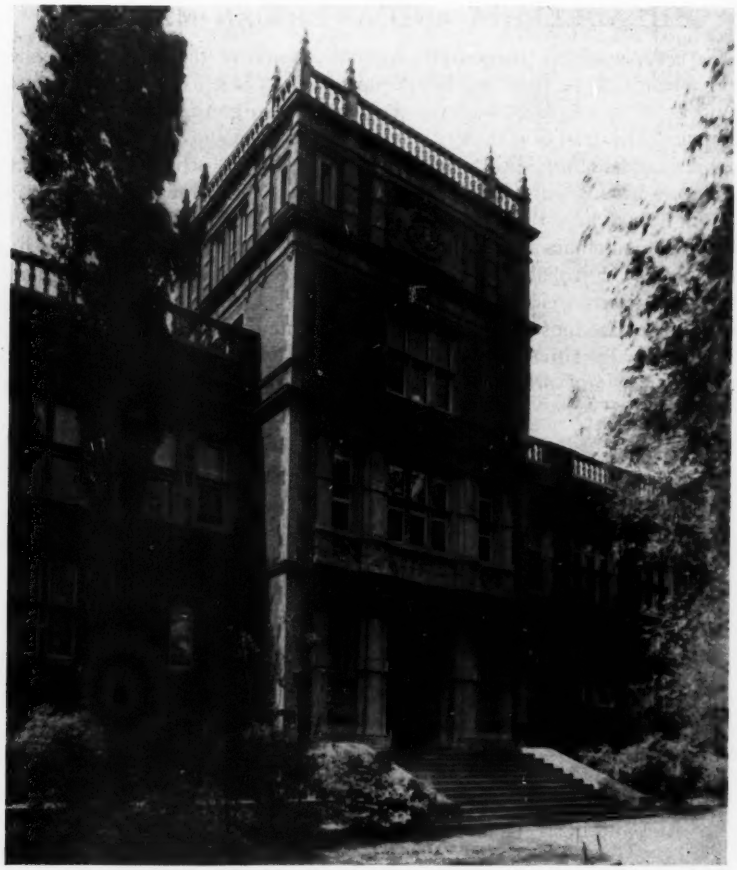
In January, 1955, there appeared the first issue of the *Journal of Chronic Diseases,* edited by Dr. Joseph Earle Moore, with Dr. David Seegal as Associate Editor. It has a distinguished editorial board. The ANNALS OF INTERNAL MEDICINE welcomes this new publication in an important field of internal medicine.

PHILADELPHIA AND AMERICAN MEDICINE

THE approaching thirty-sixth Annual Session of the American College of Physicians, to be held in Philadelphia, April 25–29, 1955, will bring the members of this College back to the cradle of organized medicine in this country. The tradition of medicine in Philadelphia is well known; Philadelphia is a famed medical center, with five medical schools, including the oldest one in the United States. Medicine has been taught and practiced on a high level here through the past two centuries. If history alone were all that Philadelphia could offer the visiting physician, however, medical meetings would probably be scheduled elsewhere. The fact is that Philadelphia's physicians welcome their colleagues today not to a city of the past, but to one of the most progressive medical centers of the world.

Strategically situated in the prosperous Delaware Valley, Philadelphia ranks in size and productivity among the great cities of the world. It

Anatomical Hall—Philadelphia 1765
Cradle of American Medical Education



Entrance to Medical Laboratories, University of Pennsylvania

compares with Chicago and New York City in the United States for first place in the number of recognized medical schools. The statistics on hospitals and physicians in the three cities are approximately in proportion to their populations. Previous reports on the historical background of Philadelphia medicine have appeared in the *Annals of Internal Medicine* of 1935 and 1946.

University of Pennsylvania School of Medicine. Looking forward to the celebration 10 years hence of its medical bicentennial, the University of Pennsylvania is today engaged in the most progressive period of expansion in its long and distinguished history. The School of Medicine, founded in 1765, was the first such institution established on the North American continent. Later, the Hospital of the University of Pennsylvania (1874)

became the first large teaching hospital to provide clinical facilities and bedside instruction for its medical students. In addition, the University's Graduate School of Medicine, dating from 1916, was the first comprehensive venture of its kind to provide postgraduate education for physicians in the various medical specialties.

Today in its 190th year of medical service, the University of Pennsylvania has added many new facilities to its physical plant within the past five years. Plans have also been formulated for further expansion in the near future to develop the Philadelphia Medical Center of the University of Pennsylvania. This center will coincide in time with the medical bicentennial celebration 10 years from now.

Construction of the Thomas Sovereign Gates Memorial Pavilion at a cost of six and one-half million dollars has been accomplished since 1950. This building, an 11-story structure located on the site of the original University Hospital, extends for nearly two city blocks and dominates the West Philadelphia campus of the University. The Gates Pavilion bears the name of a former President of the University, in recognition of his great contribution to medical expansion plans before his death on the eve of their initiation. The new Gates Pavilion is an outpatient building providing for an estimated 400,000 clinic visits annually, as compared with a former figure of 124,000 visits. Much of this increased service has resulted from centralization of administration and use of standard procedures for handling patients and their records. Related clinical laboratories and research units are also located under one roof. The University of Pennsylvania Diagnostic Clinic, located in the Gates Pavilion, is a non-profit, unincorporated association of the hospital staff. In its first year of operation it provided care for many patients referred from private physicians. The Diagnostic Clinic also conducts annual health surveys on personnel from important industrial and business organizations.

Medical Alumni Hall, another recent addition donated largely by physician-graduates of the University, provides a modern auditorium for teaching and health meetings. Seating 350 persons, its amphitheater stage is equipped with color television for transmitting operations and other procedures from the hospital's battery of 11 operating rooms.

Other new medical construction at the University of Pennsylvania includes a modern kitchen, cafeteria, laundry, and research and storage facilities. A new hospital library, independent of the medical school library, was also provided. As a result of recent hospital expansion, a total of 900 beds is now available for the care of patients. A new Rehabilitation Center dedicated to the service, teaching and research in behalf of the physically handicapped has also been inaugurated. This rehabilitation unit provides facilities for physical and occupational therapy plus living and recreational quarters.

Future plans include the erection of further research facilities, and a new in-patient building adjacent to the present surgical quarters. This in-

Hospital of the University of Pennsylvania

patient facility will be known as the I. S. Ravdin Institute, in honor of Dr. I. S. Ravdin, John Rhea Barton Professor of Surgery and Director of the Harrison Department of Surgical Research. Also planned are a new central nurses' residence and separate quarters for the Graduate School of Medicine.

The Graduate School of Medicine, which attracts student physicians from all over the world, at present shares administrative facilities with the School of Medicine and other related agencies. The Graduate Hospital of the University of Pennsylvania, a 352-bed general hospital located at

Graduate Hospital of the University of Pennsylvania

Nineteenth and Lombard Streets in central Philadelphia, is operated solely for the teaching benefit of graduate medical students.

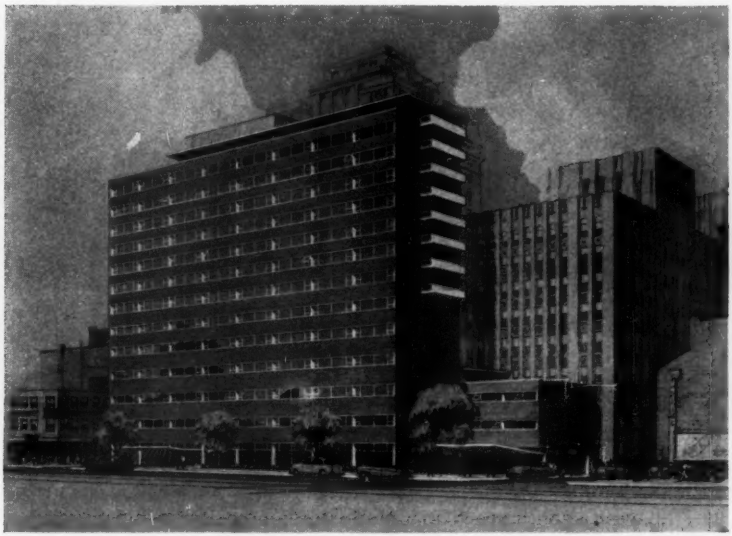
The University of Pennsylvania, with its several additional schools (the School of Auxiliary Medical Services dating from 1951, the School of Dentistry now in its 77th year, and the School of Veterinary Medicine now in its 70th year) continues to maintain its pioneer leadership in medicine and allied sciences throughout the world.

Jefferson Medical College and Hospital. Philadelphia's second oldest medical college, the Jefferson Medical College, was founded in 1825. Its first class was graduated the following year. In the intervening 130 years it has conferred a medical degree upon approximately 19,000 students. The college has stressed clinical training since its earliest days. Until recently it was the largest of the nation's medical schools, and its graduate body of over 6,300 alumni physicians is thought to constitute the largest such group in the United States.

The College today occupies modern buildings on Walnut Street, just west of Tenth Street, in central Philadelphia. In addition to the Doctorate in Medicine, the College offers graduate studies in the medical sciences leading to M.S. and Ph.D. degrees. The present College Building is adjacent to the College Hospital and the Curtis Clinic for outpatients, dedicated in 1931.

Attached to the hospital's Thompson Annex is the new 14-story Jefferson Medical College Hospital Pavilion. This Pavilion, located at Eleventh Street between Walnut and Sansom Streets, was completed recently at a cost of seven and one-half million dollars. In operation since formal dedication ceremonies on November 8, 1954, this addition expands the institution's various divisions to nearly 1,200 beds, making it the third largest voluntary hospital in the United States.

The new Pavilion, a 300-bed, ultra-modern hospital, will accommodate approximately 8,500 additional patients yearly. This will enable Jefferson to serve upwards of 30,000 bed-patients annually. There are seven nursing



Jefferson Medical College Hospital

floors in this latest unit, one devoted exclusively to maternity patients. Fourteen operating rooms on two floors enable the hospital to centralize all of its operating facilities in the new building. Expanded radiology and clinical laboratories also occupy individual floors. Another floor for gynecology and obstetrics includes four operating rooms, four delivery rooms and three labor rooms. The latest type of x-ray equipment has also been installed, some designed especially for the new addition.

The completely air-conditioned and fireproof building of functional hospital design is served by a new laundry, kitchen and supply facilities designed especially for patient comfort. This latest unit at the Jefferson Medical College Hospital emphasizes the continued excellence of one of the nation's oldest and best-known medical institutions. Together with its affiliated specialized hospitals, institutes and allied hospitals, it forms with the college the Jefferson Medical Center.

Hahnemann Medical College and Hospital. The Hahnemann Medical College and Hospital of Philadelphia is the result of a successive union of three older institutions, one of which was founded in 1848. The charter

Hahnemann Medical College and Hospital

bearing the institution's present name dates from 1885. In 1886 the Hahnemann Medical College and Hospital located at its present site in central Philadelphia. The buildings of this center now cover a two and one-half acre tract between Broad and Fifteenth Street, extending from Race to Vine Streets. The present 600 bed Hahnemann Hospital is a modern 19 story structure facing North Broad Street. The medical college occupies part of the former hospital, in addition to a modern seven-story building facing Fifteenth Street. The latter building houses most of the teaching classrooms, laboratories and research facilities. It also contains the Klahr Auditorium, which has a seating capacity of 1,200. The Hahnemann Clinic Building on Race Street, erected in 1945, houses clinic facilities for the diagnosis and treatment of ambulatory patients.

Founded as a homeopathic institution, Hahnemann for the past 50 years has presented a curriculum which parallels those of other regular medical schools. Since 1946, instruction in homeopathy has been included only on an elective basis. In addition to the curriculum leading to the Doctor of Medicine degree, the Hahnemann Medical College and Hospital offers graduate programs in the basic medical sciences and has schools of nursing, medical and x-ray technology.

Since 1946 also, a general reorganization of the curriculum has been effected. Clinical clerkships in the third and fourth years have largely replaced the older lecture method of instruction. Correlation conferences have been initiated in the first two years to integrate the basic sciences into clinical teaching. Laboratory exercises have also been modernized to correlate clinical study of disease processes.

To extend clinical teaching facilities, outside hospital affiliations have been added to the medical school program. Hahnemann Medical College and Hospital now has affiliations with the Albert Einstein Medical Center, Southern Division; the Memorial Hospital of Wilmington, Delaware; the Harrisburg Hospital, and the Guthrie Clinic of Robert Packer Hospital at Sayre, Pennsylvania. These "major" affiliations cover nearly all the teaching services in medicine, pediatrics, surgery, obstetrics and gynecology. In addition, other affiliations have been made for special training in psychiatry, tuberculosis and geriatrics. These affiliations are closely integrated with the medical college through a Director of Education in each hospital. The medical student resides at the affiliate hospital and there enjoys a wider range of patient care and closer contact with his instructors.

A Student Research Society is active in the medical college. Students are encouraged to devise and work upon problems in the research laboratory under departmental supervision. To encourage student research activities when academic sessions are not being held, small fellowships are provided to afford financial aid to those students who could not otherwise devote time to research. An annual Student Research Day is held for presentation of original papers. Several of these papers have been published in various scientific journals.

Hahnemann now has a student body of approximately 400. It accepts women students and places no restrictions on race, creed or color in admissions. The freshman class is limited to 108 members, the optimal number for which the faculty can provide the highest grade of instruction. Beginning in the academic year 1955–1956, a few transfer students will be accepted at the third year level. This desirable feature had been deferred until the administration considered its modernization program to be working with sufficient efficiency to train additional students adequately in the clinical years.

Modernization of physical facilities at the college has been under way for several years. This program will eventually provide for replacement of the present structure now used by the college. In its place a modern building is planned to house classrooms, laboratories and research areas, thereby permitting a larger student body and faculty in the future.

Woman's Medical College of Pennsylvania. The Woman's Medical College of Pennsylvania, founded in 1850 at Philadelphia (as the Female Medical College of Pennsylvania), was the first college in the world regularly organized for the medical education of women. Assuming its present name in 1867, it is still the only medical school in the United States exclusively for women.

The opening session of the College found 40 students enrolled under a faculty of six men. The first class to be graduated numbered eight, of

Woman's Medical College of Pennsylvania

whom one, Dr. Ann Preston, was soon appointed to the faculty. Today, over two thirds of the faculty are women.

The site and buildings of the present Woman's Medical College and Hospital, opened in 1930, occupy approximately 10 acres at Henry Avenue and Abbottsford Roads. The Hospital of the Woman's Medical College of Pennsylvania, containing 207 beds, is conducted under the professional direction of the college faculty. A fully equipped heart clinic was opened in 1932 and a bronchoscopic clinic in 1934. Out-patient clinic services are provided at the Barton Dispensary, 1309 North Twenty-Second Street, as well as at the Hospital. Affiliated clinical teaching is also conducted in the wards and clinics of the Philadelphia General Hospital, the Woman's Hospital, Pennsylvania Hospital, and the Memorial Hospital at Roxborough. Recent additions to the Medical College Hospital include Ann Preston Hall (1953), providing quarters for resident physicians, medical students, and student and graduate nurses; also the Martha Tracy Memorial, a recently added wing (1954), used for preventive medical care.

Temple University School of Medicine. Temple University, founded by Russell H. Conwell, the noted Philadelphia clergyman, educator and humanitarian, celebrated its seventieth anniversary last year. The seal of Temple University bears the motto *Perseverentia vincit,* a motto well exemplified in the rapid progress of its medical school, opened in 1901. Although it is the newest of Philadelphia's five recognized medical schools, its status today among the finest medical institutions in the world is uncontested.

Coeducational since its inception and the first coeducational medical school in Pennsylvania, it included two women in its third graduating class. More recent outstanding medical achievements include the work of the

Temple University Medical Center

world-famous Chevalier Jackson Bronchoscopic Clinic, the Agnes Barr Chase Surgical Research Foundation, the Samuel S. Fels Medical Research Institute and the Institute of Public Health and Preventive Medicine of Temple University. Advances such as the establishment of the first psychosomatic medical clinic in the United States and the development of procedures in electrokymography, thalamotomy and stereofluoroscopy may be mentioned among Temple's contributions to American medicine.

The eight-story medical school building, opened in 1930, is situated at North Broad and Ontario Streets, directly opposite the Temple University Hospital. The new Temple University Medical Center, now under construction in north Philadelphia adjacent to the present hospital, attests remarkable growth from the original 12-bed Samaritan Hospital of Temple College (1891). The new medical center, costing ten and one-half million dollars, includes a 10-story in-patient building, an eight-story out-patient building, and a four-story auxiliary-services building. The latter will house the main kitchen and cafeteria, diagnostic and therapeutic departments for radiology and clinical pathology, and a surgical pavilion consisting of 12 operating rooms, anesthesia induction and recovery rooms. The present 600-bed capacity of the Temple University Hospital will be expanded to 1,000 beds upon completion of the new medical center buildings next year.

Other integral divisions of the Temple University Medical Center are its separate pediatric unit, the St. Christopher's Hospital for Children, and District Health Center Number Eight, operated in coöperation with the Philadelphia Department of Health. In addition, teaching affiliations with Episcopal, Philadelphia General, Skin and Cancer, and Shriner's Hospitals are supplemented by other affiliations with the Albert Einstein Medical Center, Northern Division, and the Eagleville Sanatorium for Chest Diseases.

Hospitals

The hospitals directly connected with the various schools of medicine have already been mentioned. Of the many other Philadelphia hospitals we briefly note those which will be most intimately involved with the forthcoming college meetings.

The Pennsylvania Hospital. To those who have the good fortune to appreciate medicine in its historical perspective, the Pennsylvania Hospital affords a rich source of inspiration. One of the largest and most important hospitals in Philadelphia today, it still retains much that is evocative of its long and notable past. It is, in fact, the oldest hospital in the United States which was intended wholly for the care of the sick and wounded and which has continued on its original site carrying its original name.

The founding of the Pennsylvania Hospital in 1751 was largely accomplished through the efforts of Benjamin Franklin and his friend, the physician Thomas Bond. The roster of the hospital has always contained the names of many of the city's leading physicians. The present divisions of the Pennsylvania Hospital are the Department for the Sick and Injured

(including the Benjamin Franklin Diagnostic Clinic), the Department for Mental and Nervous Diseases, and the Institute of the Pennsylvania Hospital. The Philadelphia Dispensary, founded in 1786, is now also carried on as part of the "Out-Patient Department of the Pennsylvania Hospital and Philadelphia Dispensary."

The Department for the Sick and Injured, at Eighth Street between Spruce and Pine Streets, occupies the first permanent hospital site (1755). This department of the Pennsylvania Hospital, like its centrally located neighbors, Jefferson and Hahnemann Hospitals, fulfills the extraordinary demands made upon downtown hospitals in a large metropolis.

The Department for Mental and Nervous Diseases and the Institute serve as reminders that the Pennsylvania Hospital from its earliest days

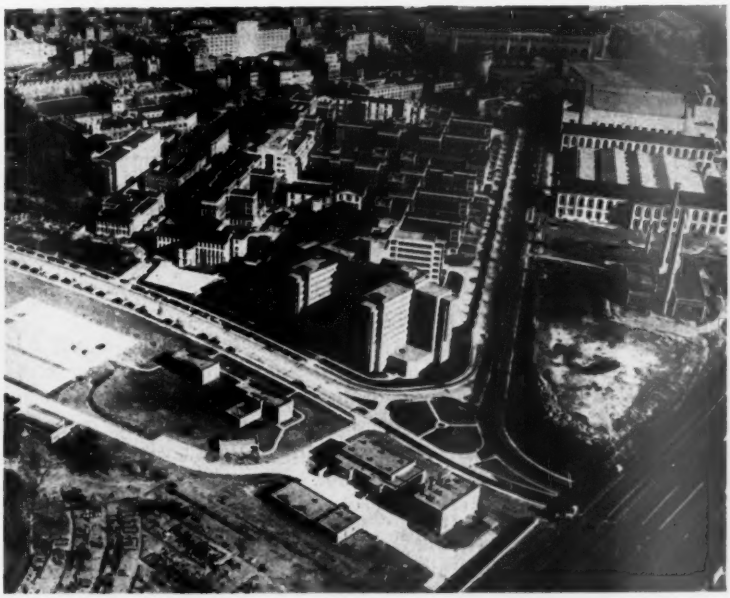
Pennsylvania Hospital

was the pioneer in this country in the humane treatment of the mentally ill. This Department was moved to its present site in West Philadelphia, at Forty-Fourth and Market Streets, in 1841. Its first superintendent, Dr. Thomas S. Kirkbride, so impressed his personality upon the institution during his long service there that for many years it was familiarly known as "Kirkbride's."

The Institute at Forty-Ninth and Market Streets represents the Hospital's latest development in the care of mental disease. Its primary purpose is the prevention of mental and nervous illness. The long career of the Pennsylvania Hospital has been memorable in many ways, in none other perhaps so memorable as in its steady devotion to the understanding and healing of the mentally ill as well as the physically sick and injured.

Philadelphia General Hospital. The Philadelphia General Hospital dates its origin from the Philadelphia Almshouse, established in 1729. The history of this institution—from its earliest days as an alms- (or "bettering") house, receiving the poor, sick and insane, to its position today as the largest hospital in the city (2,628 beds)—forms a remarkable chapter in American medicine.

The first Almshouse, erected in 1731 in old Philadelphia, officially adopted the title "Philadelphia Hospital" in 1935, shortly after moving to its present site in West Philadelphia. In 1834 it assumed unofficially the name "Blockley," from the township in which it was placed. This



Philadelphia General Hospital—Blockley Division

became the name by which it has been commonly known. The present title, Philadelphia General Hospital, was officially adopted in 1902.

The Philadelphia General Hospital, owned and supported by the City of Philadelphia, now consists of two divisions. The Blockley Division at 34th and Curie Avenue has 2,093 beds and treats medical, surgical, tuberculous, obstetric, pediatric, psychiatric and neurologic patients. The second unit, the Northern Division of the Philadelphia General Hospital (formerly the Philadelphia Municipal Hospital for Contagious Diseases), is located at Front and Luzerne Streets in North Philadelphia. It has 536 beds devoted to the care of contagious diseases, and to obstetric, gynecologic and tuberculous patients.

An extensive multimillion-dollar renovation and building program is currently under way at the Philadelphia General Hospital. About half has been completed to date. The modern 700-bed Mills Building at Blockley, opened in 1951, is a model of advanced hospital planning. Named in honor or Dr. Charles K. Mills, pioneer Philadelphia neurologist, it houses both medical and neurologic services. A five-story Food Service Building was opened in March, 1954; this is a model institutional service unit. In addition, new quarters for the hospital laboratories, heart station and medical library have recently been completed. Other projects now in the planning stage include improved operating rooms and x-ray, out-patient and maternity department facilities.

The Philadelphia General Hospital is well known for the great variety of services it offers, and as a teaching center. Its present daily in-patient census is about 2,000. In addition, approximately 140,000 out-patient visits are made to the hospital each year. Playing a vital rôle in medical education, the hospital is closely affiliated with the five Philadelphia medical schools. The hospital staff now includes about 550 members, most of whom are faculty members at the affiliated medical schools. As of July 1, 1954, the house staff comprised 108 interns and 87 resident physicians and fellows.

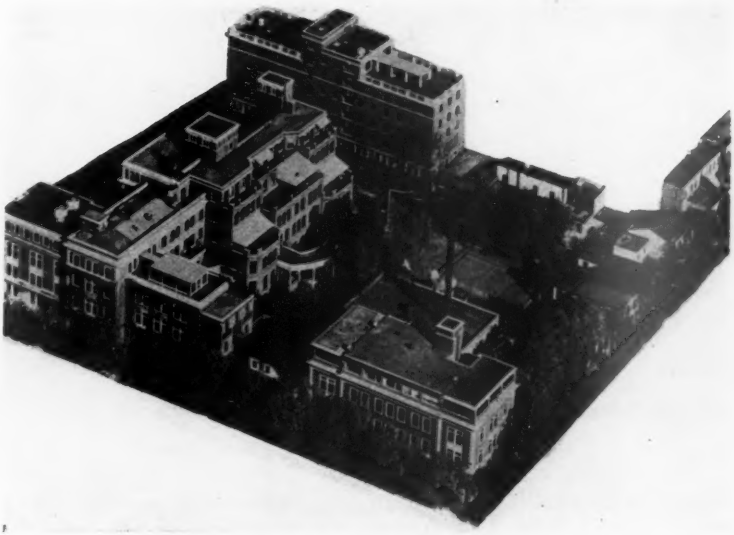
The Children's Hospital. The Children's Hospital of Philadelphia, at Eighteenth and Bainbridge Streets, is the oldest in America specifically devoted to the care of children. The third hospital in the world designed exclusively for children, it is celebrating its centennial this year.

During the past year there were over 5,700 admissions and nearly 39,000 visits at the out-patient unit. The latter includes some 26 different services. A clinical teaching and research institution, the Children's Hospital features all the facilities necessary to a modern medical center. It is one of three hospitals in this country where pediatric surgery and anesthesia are taught in a specialized resident training program.

Recent growth of the surgical services is evidenced by the opening last year of four new operating rooms. A large Research Department employs a staff of 100 scientists, including research fellows from many foreign countries. Major advances in the knowledge of virus diseases, rheumatic fever, blood dyscrasias, kidney disease and nutrition have stemmed from Children's Hospital. A large portion of this research activity is now housed in a modern six-story building opened in the spring of 1954.

Early in 1952, the Children's Hospital spearheaded a movement to affiliate with other child care agencies in an organization known as the Children's Medical Center, Incorporated. To date the Philadelphia Child Guidance Clinic, Oakbourne Colony Hospital, the Society for the Prevention of Cruelty to Children, and the Children's Hospital of Philadelphia have entered this Medical Center. Other related agencies are now considering such affiliation to enhance the scope and service of this center.

Albert Einstein Medical Center. The Albert Einstein Medical Center of Philadelphia represents the consolidation of three hospitals and a com-



Children's Hospital

munity health center. Consolidation of the 98 year old Jewish Hospital, now the Northern Division, the 53 year old Mt. Sinai Hospital, now the Southern Division, and Northern Liberties Hospital, now the Eastern Division, took place in 1952.

A modernization and reconstruction program, launched upon consolidation, is still in progress. Modernization of facilities at the Southern Division, at a cost of one and a half million dollars, is now under way. This project will provide that division with a total of 345 beds.

At the Northern Division, a new out-patient department and a new general hospital building, to cost eight million dollars, are planned. A new School of Nursing building is nearing completion at the present time.

Eventual objective of this expansion program at the Einstein Medical Center is the development of two major divisions, a total of 1,000 beds, a modern School of Nursing, and major medical research and teaching facilities. Much of this objective has already been accomplished. With 714 beds and 110 bassinets in all divisions at present, future expansion is geared to keep apace of community needs at this large medical center.

Lankenau Hospital. The Lankenau Hospital, incorporated in 1860, opened for patients in 1866 as the German Hospital of the City of Philadelphia. The present name honors its second President, John D. Lankenau, whose personal care and generosity are credited as among the chief agents through which the hospital reached its present high standing among the city's hospitals.

At its former location, Girard and Corinthian Avenues, the Lankenau

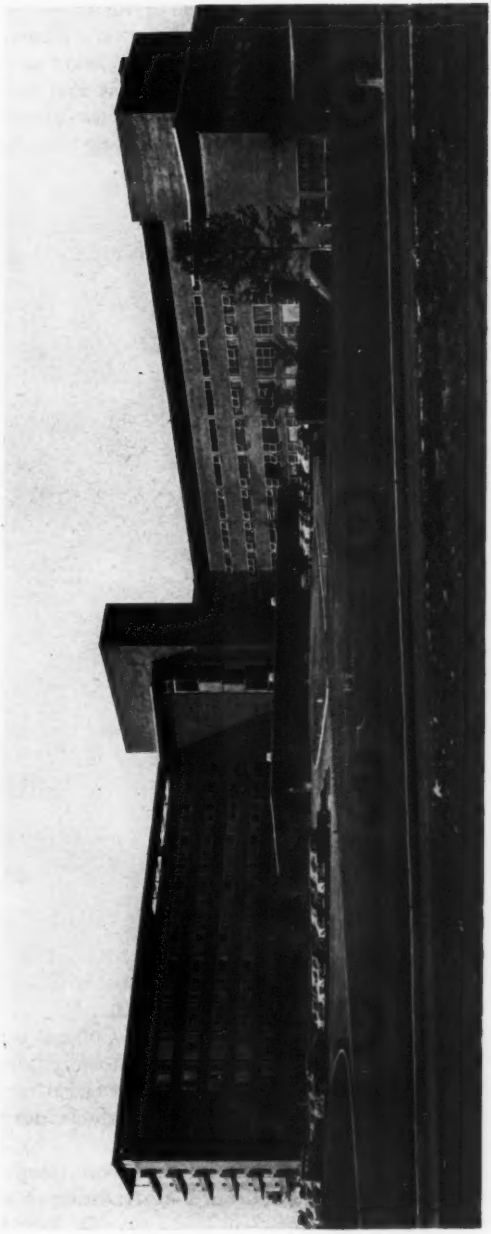
Albert Einstein Medical Center—Northern Division

Hospital grew steadily until necessary expansion was no longer possible there. Surveys showed that a general hospital was needed in the Overbrook area, just outside the city line. The former Overbrook Golf Club property was therefore purchased by Lankenau as an obvious choice for the new hospital and health center.

Situated on 92 acres of beautiful rolling land, the new, ultra-modern Lankenau Hospital and Health Center at Lancaster Avenue above City Line was completed in December, 1953. At that time more than 150 patients were moved from the old buildings to the new $10,300,000 hospital. With a capacity of 260 beds, the new Lankenau Hospital is one of the most modern medical institutions in the world. Equipped to offer the best possible service to patients, it incorporates many time-saving devices for its medical and nursing staff. In an underground room surrounded by rock and earth is the Cobalt-60 rotational therapy unit, or Theratron, for the treatment of malignancies. A community health education program is made possible through exhibits in the modern Health Museum, together with special educational programs in the 335-seat auditorium. Here both professional and non-technical information on health and medical matters is presented to interested audiences.

Presbyterian Hospital. The Presbyterian Hospital, incorporated in 1871 and opened to patients in the following year, is a general hospital now having 329 beds and 42 bassinets. Located at Thirty-Ninth Street and Powelton Avenue in West Philadelphia, the hospital offers complete in-patient services in addition to providing 26 clinics for out-patients. The Board of Trustees of the hospital also operates Cathcart Home in Devon, Pennsylvania, a nursing home for the chronically ill and infirm.

As one part of an intensive building campaign, a new Thoracic and Cardiovascular Research Laboratory was dedicated at the Presbyterian



Lankenau Hospital

Hospital in June, 1954. The staff of these laboratories includes specialists in all phases of thoracic and cardiovascular diseases. Extensive research is now in progress on problems in these and other fields of medicine and surgery. In addition, modernization of the pediatric and surgical department facilities has been accomplished recently, plus the erection of a new student nurses' residence. An active medical teaching program is also in effect at the Presbyterian Hospital, largely in affiliation with the University of Pennsylvania School of Medicine.

Germantown Dispensary and Hospital. The Germantown Dispensary and Hospital will celebrate its eighty-fifth anniversary in May, 1955. Lo-

Presbyterian Hospital

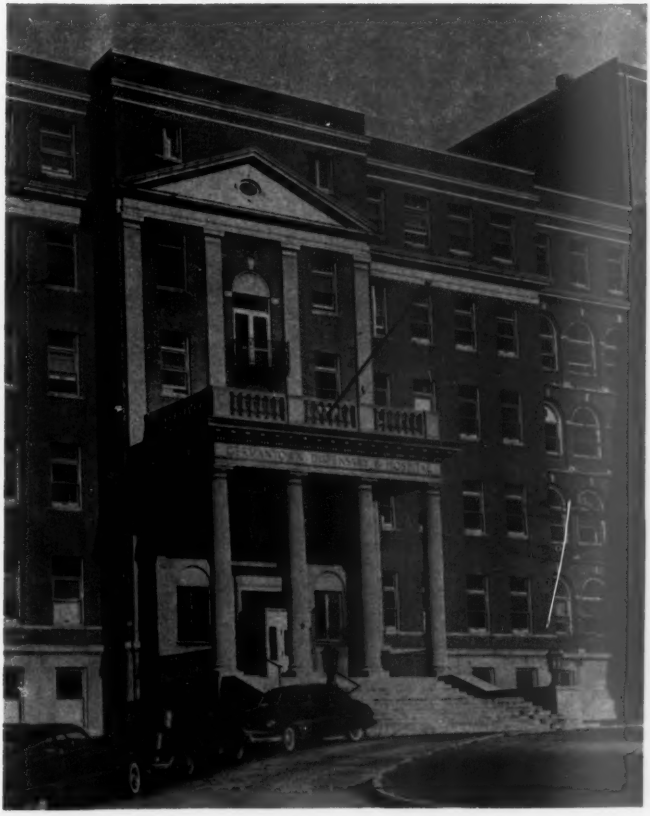
cated at East Penn and Wister Streets in Germantown, it now has a total capacity of 311 beds. Starting as a small dispensary in 1870, the hospital last year totaled over 100,000 in-patient days.

Recent affiliation with the Jefferson Medical College has added the teaching methods and clinical experiences of nationally known medical teachers and clinicians. The steady progress of the Germantown Hospital in service to Philadelphia has placed it in an enviable position in contemporary medicine.

U. S. Naval Hospital. The present U. S. Naval Hospital of Philadelphia, commissioned in 1935, continues a long tradition of service established by the Navy medical department in this city. Occupying an area of

48 acres at Broad Street and Pattison Avenue in South Philadelphia, the hospital has an authorized bed capacity of 1,200. Patients treated consist of active duty and retired members of all the Armed Forces, their dependents, and beneficiaries of the Naval Home and the Veterans Administration.

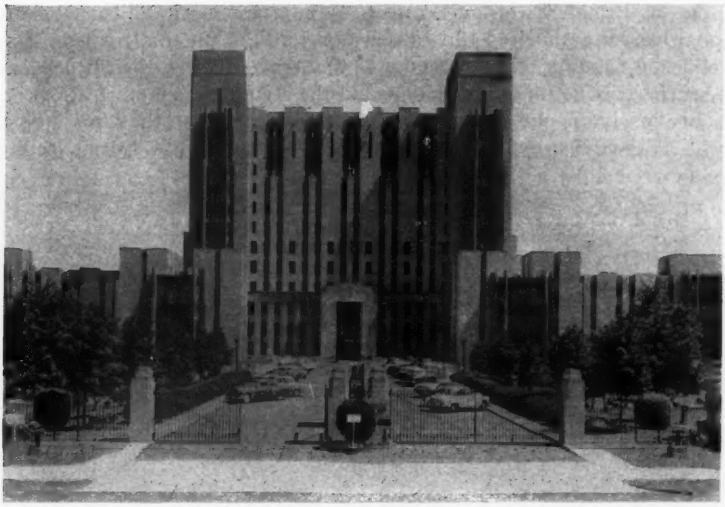
This hospital is one of the major teaching hospitals of the United States Navy. Although primarily a general hospital, it also has special facilities



Germantown Dispensary and Hospital

for the rehabilitation of amputees, aural rehabilitation, use of radioactive isotopes, and the treatment of neuropsychiatric disorders. A teaching liaison with the medical schools and several other hospitals in the Philadelphia area is maintained by visiting civilian consultants and appointment of naval medical officers to medical school faculties.

Veterans Administration Hospital. The Veterans Administration Hospital, located at University and Woodland Avenues in West Philadelphia,



U. S. Naval Hospital

renders service to eligible veterans in Philadelphia and vicinity. Construction of this modern medical center was completed late in 1952, and the hospital was officially dedicated on December 7, 1952.

A general medical and surgical hospital with a capacity of 488 beds, it has the following subdivisions: 262 medical, 180 surgical, 38 neuropsychiatric, and eight physical medicine beds. There are also a medical re-

Veterans Administration Hospital

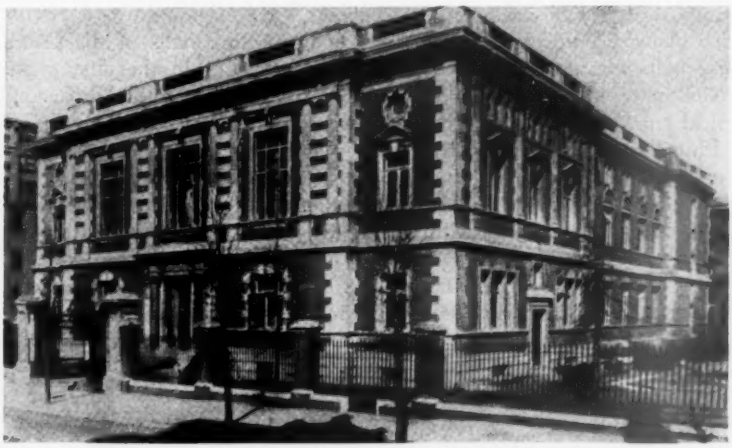
search laboratory, radioisotope unit, and plastic eye and restorations clinic in the central building. During the past year the average daily census was 430 patients, with a total of 156,774 patient days during the year.

The Veterans Administration Hospital is affiliated with all the Philadelphia medical schools through a Dean's Committee composed of the dean of each of the five schools. This Committee functions in an advisory capacity to coördinate educational and medical research activities, appointment of consultant and attending staff, and direction of the residency training program. Regularly scheduled conferences and lectures are held in the various specialties, together with clinical-pathological conferences and journal club meetings. The consulting and attending staff takes an active part in all these activities and contributes much to the hospital's educational program.

Medical Organizations. It is to be expected that a city so rich in medical institutions and tradition should be rich also in medical societies. Over 50 such organizations announce their meetings in the weekly roster, *Philadelphia Medicine,* published by the Philadelphia County Medical Society. Two of these medical organizations must be especially mentioned.

The largest in the city is the Philadelphia County Medical Society, with headquarters at 301 South 21st Street. Organized in 1849, this Society has been from its beginning an active and effective medical organization serving physicians and public alike. In addition to its own scheduled medical meetings, the weekly publication of this body comprises a reliable guide to the numerous activities of the city's medical societies.

The College of Physicians of Philadelphia, organized in 1787, is the oldest existing and most famous medical society in the city. Its present quarters at 19 South 22nd Street were erected in 1909. This College houses one of the finest medical libraries in the world as to both size and



College of Physicians of Philadelphia

Headquarters, American College of Physicians

quality. Its medical historical and text collection is among the finest, as are the comprehensive files of medical periodicals from all over the world. Expansion of the present library facilities is now in progress. The College holds monthly scientific meetings (except during the summer), often with distinguished guest speakers. Its Fellows have organized five Sections which likewise hold monthly meetings in the lecture halls of the College. These halls are also used by other medical societies in the city, making the College of Physicians of Philadelphia a true center for the "diffusion of medical knowledge," its originally stated purpose.

Philadelphia medical activities today also include the publication of over 20 medical journals. This city is home to five of the largest medical publishing houses in the world. Here the headquarters of the American College of Physicians was established in 1926; its present attractive location is at 4200 Pine Street.

Philadelphia, one of the nation's most historic and interesting cities, today teaches and practices medicine with a devotion that combines modern skill with a rich inheritance from the past. It is without doubt one of the truly great medical centers of the world.

FRED B. ROGERS, M.D.,
For the Committee on Publicity

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Thirty-sixth Annual Session

PHILADELPHIA, PA.

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INVITATION

You are most cordially invited to attend the 36th Annual Session of the American College of Physicians, to be held in Philadelphia, April 25–29, 1955.

The physicians of the Philadelphia area are delighted to serve as hosts on this occasion. They are happy to make available the facilities, medical and otherwise, of a city intimately associated with the origin of American traditions and holding a position in the foremost ranks of American medicine since colonial times. We are justly proud of our outstanding hospitals and five medical schools—Hahnemann Medical College, Jefferson Medical College, Temple University School of Medicine, University of Pennsylvania School of Medicine and Woman's Medical College. Recently completed, or in the process of construction, are many new hospital buildings, designed in accordance with the latest developments in the science of hospital architecture, and equipped with every facility to make readily available the most modern methods of treating disease. Also located within the city are the fine buildings housing our

American College of Physicians' home office, and that of the College of Physicians of Philadelphia. The latter is a venerable and revered institution which dates back to 1787, and contains an excellent medical museum in addition to one of the world's finest medical libraries. It is to be hoped that the members and guests of the College will avail themselves of the opportunity to visit these institutions during their stay in our city.

We Philadelphians are likewise proud of our many non-medical attractions. These include Independence Hall, the Liberty Bell, Valley Forge, old Christ Church, the Betsy Ross House, and many other items of historical and patriotic interest. In addition to these there are the famous Franklin Institute, the Fels Planetarium, the Art Museum, etc.

This year's program is replete with carefully selected lectures, symposia, panels, clinical-pathological conferences, television demonstrations and hospital clinics. An entirely new feature will be a clinical-*physiological* conference, which will discuss cases from the standpoint of the contribution to diagnosis and management of newer studies of disturbed physiology. There will also be a session devoted to series of papers on recent developments in basic research, another new feature in a College program. The hospital clinics will all be located near, or in Convention Hall, thus avoiding long journeys through city traffic. All of the participants in the program have been selected both from the standpoint of their knowledge and teaching ability.

The entertainment features include a concert by the world-famous Philadelphia Orchestra under the baton of Eugene Ormandy, a reception for new members, the Convocation and President's Reception, and the Annual Banquet. At the latter, we are to have the privilege of hearing the renowned Temple University Concert Choir, under the direction of Mrs. Elaine Brown, and our speaker is to be Mr. Ogden Nash, whose writings have entertained millions the world over. The women's program includes a visit to the famous Winterthur Museum in Wilmington, a fashion show and tea at John Wanamaker's store, a lecture and show at the Planetarium, and a tour through Fairmount Park, including a visit to some old houses that have charmed so many thousands since their opening to the public.

We are sure that attendance at this year's meeting will be an experience long to be remembered. We look forward to seeing you and assure you that our every effort will be to make your stay a profitable and pleasurable one.

GENERAL INFORMATION

HEADQUARTERS

Registration headquarters, the information bureau, technical exhibits, general sessions, morning lectures and symposia, panel discussions, clinical-pathological conferences, televised clinics, certain of the hospital clinics, and meetings of Committees, of the Board of Regents and of the Board of Governors, will be held at Convention Hall, 34th Street below Spruce, Philadelphia, Pa. The Philadelphia Symphony Orchestra Concert will be held at the Academy of Music, Broad and Locust Streets, Philadelphia.

HOTEL ACCOMMODATIONS

The following hotels will be official hotels for the session. The Benjamin Franklin and the Bellevue-Stratford Hotels will be official headquarters. An A.C.P. Housing Bureau, conducted under the Philadelphia Convention and Visitors' Bureau, 17th and Sansom Streets, Philadelphia, Pa., will handle all hotel reservations. Members and guests may utilize the official reservation form accompanying the program. Additional copies of the hotel reservation form may be obtained from the Executive Secretary of the College, 4200 Pine Street, Philadelphia 4, Pa.

LIST OF HOTELS

Hotel	Size (Rooms)	For One Person	For Two Persons		Suites
			Double Bed	Twin Beds	
Adelphia 13th & Chestnut Sts.	262	$6.50–$7.00	$ 9.50–$12.00	$10.50–$12.50	$30.00
*Bellevue-Stratford Broad & Walnut Sts.	485	5.50– 7.50	9.00– 11.00	11.00– 15.00	20.00– 30.00
John Bartram Broad & Locust Sts.	190	6.50	9.00	11.00	25.00
*Benjamin Franklin 9th & Chestnut Sts.	885	6.00– 9.00	9.00– 12.00	13.00– 15.00	20.00
Drake 1512 Spruce St.	125		8.00	10.00– 13.00	16.00– 18.00
Essex 13th & Filbert Sts.	144	5.00– 6.50	10.00	12.00	30.00
Normandie 36th & Chestnut Sts.	100	4.00	7.00	8.00	10.50– 12.00
Penn Sherwood 39th & Chestnut Sts.	350	5.50– 6.00	9.00– 10.00	10.00– 12.00	15.00– 20.00
Robert Morris 17th & Arch Sts.	75	5.00– 5.50	7.00– 8.00	8.00	
St. James 13th & Walnut Sts.	100		7.00– 9.00	9.00– 10.00	15.00
Sylvania Locust east of Broad St.	270	7.00– 7.50	Triples $15	11.50– 14.00	22.00
Walnut Park Plaza 63rd & Walnut Sts.	24		10.00	11.00	14.00

* Headquarters Hotels.

Who May Register—

(*a*) All members of the American College of Physicians in good standing for 1955.

(*b*) All newly elected members.

(*c*) Graduate medical students pursuing courses in local institutions of Philadelphia, including residents in Philadelphia hospitals, without registration fee, **upon presentation of matriculation cards or other evidence of registration at these institutions**; admission to exhibits, general sessions, morning lectures, clinical-pathological conferences and TV clinics.

(*d*) Members of the staff, including interns, of the Philadelphia Hospitals participating in the program, without registration fee, **upon presentation of proper identification**; admission to exhibits, general sessions, morning lectures, clinical-pathological conferences and TV clinics (this does not include courtesy staff members).

(*e*) Bona fide hospital residents, regardless of their location in North America, without registration fee, **upon presentation of proper credentials from**

their hospitals; admission to exhibits, general sessions, morning lectures, and other program features where facilities are adequate.

(*f*) Members of the Medical Corps of the Army, Navy, Public Health Service, Air Force and Veterans Administration, either of the United States or Canada, without registration fee, **upon presentation of proper credentials.**

(*g*) Qualified physicians, who may wish to attend this Session as visitors, sponsored in advance by letter or in person by a member of the College; such physicians shall pay a registration fee of $25.00, and shall be entitled to one year's subscription to the ANNALS OF INTERNAL MEDICINE (in which the proceedings will be published) included within such fee.

(*h*) Full-time medical teachers holding the rank of Assistant Professor or lower, **upon presentation of proper credentials from their medical schools,** shall be entitled to a reduction in the registration fee to $12.50.

The above regulations are essential because of the increasingly large attendance at the Annual Sessions of the College, and the necessity of accommodating members first.

Registration Bureau—While official registration will start on Monday morning, April 25, advance registration of members and exhibitors will be provided for by mail. The Registration Bureau will be set up for advance registration at Convention Hall on Sunday, April 24, from 2:30 P.M. to 5:00 P.M. The Registration Bureau, located on the Exhibition Floor of Convention Hall, will be open throughout the week from 8:45 A.M. to 5:30 P.M.

Advance Registration of Members—In order to facilitate quick registration at the meeting for members of the College, an advance registration form, with directions, will be enclosed with the formal Program to all Fellows and Associates. The success and justification of the plan is wholly dependent upon the co-operation of members, and thus the directions should be carefully noted and the proper forms returned to the Executive Offices of the College long in advance, so that each member's envelope of forms and badge will be ready for him when he calls at the Advance Registration Window. The use of this form will eliminate long lines and delays so frequently encountered at large Conventions. A member, however, should not send in this form unless he is sure he is going to be present.

Registration Blanks for all Panel Discussions and Clinical-Pathological Conferences will be enclosed with the final program to members of the College. Non-members will secure registration blanks at the Registration Bureau during the Session.

Daily Bulletins—A Daily Bulletin of registrations will be published at this meeting.

Bulletin Board for special announcements will be located near the Registration Bureau.

Transportation—Local transportation arrangements are in charge of the Committee on Hotels and Transportation, which will issue information at the meeting. Taxicabs are recommended in connection with the hospital clinics at the following hospitals: Children's Hospital, Graduate Hospital, Hahnemann Hospital and Veterans Administration Hospital. A special bus will operate from the Benjamin Franklin and Bellevue Stratford Hotels to the special clinic at the Lankenau and U. S. Naval Hospitals. Regular busses will operate from the Benjamin Franklin and Bellevue Stratford Hotels directly to Convention Hall, with convenient stops for those attending clinics at the Hospital of the University of Pennsylvania and at the Philadelphia General Hospital. The Jefferson Hospital and the Pennsylvania Hospital are near the Benjamin Franklin Hotel, requiring only a few minutes' walk.

The Annual Business Meeting of the College will be held at 2:00 P.M., Thursday, April 28, immediately preceding the afternoon general session. All Masters and Fellows of the College are urged to be present. There will be the election of Officers, Regents and Governors, the annual reports of the Secretary-General, Executive Secretary and Treasurer. Announcements will be made of the Research Fellowship Awards, Latin-American Fellowship Awards, the A. Blaine Brower Traveling Scholarship Awards, the Elizabeth Archbold Bowes Traveling Scholarship Award and the Mead Johnson Postgraduate Scholarship Awards. The President-Elect, Dr. George F. Strong, Vancouver, B. C., will be inducted into office.

BOARD AND COMMITTEE MEETINGS

All meetings will be held at Convention Hall at times and places indicated. Special meetings will be announced and posted.

A **Reception and Dinner** of the members of the Board of Regents, Board of Governors, Committee Chairmen, distinguished guests, and their wives, will be held Sunday, April 24, at 7:00 P.M., in the Garden Terrace, first floor, Benjamin Franklin Hotel.

Committee on Nominations

(At the call of the Chairman)

Committee on Credentials

Friday, April 22, 1:00 P.M., Room No. 101, Exhibition Floor

Committee on Credentials

Saturday, April 23, 9:30 A.M., Room No. 101, Exhibition Floor

Committee on Educational Policy

Saturday, April 23, 10:00 A.M., Room No. 200, Auditorium Floor

Committee on Insurance

Saturday, April 23, 11:30 A.M., Room No. 200, Auditorium Floor

Joint Commission on Accreditation of Hospitals—Committee on Criteria

Saturday, April 23, 2:00 P.M., Room No. 200, Auditorium Floor
Reconvene: Sunday, April 24, 9:00 A.M., Benjamin Franklin Hotel

Committee on Public Relations

Saturday, April 23, 2:00 P.M., Room No. 101, Exhibition Floor

Committee on Postgraduate Courses

Saturday, April 23, 3:00 P.M., Room No. 101, Exhibition Floor

Committee on Medical Educational Films

Saturday, April 23, 4:00 P.M., Room No. 200, Auditorium Floor

Committee on Latin-American Fellowships

Saturday, April 23, 4:00 P.M., Room No. 101, Exhibition Floor

Committee on Finance

Saturday, April 23, 5:00 P.M., Executive Secretary's Office, Exhibition Floor

Reference Committee on Blue Shield and Other Health Plans

Sunday, April 24, 9:00 A.M., Room No. 200, Auditorium Floor

Editorial Board, Annals of Internal Medicine

Sunday, April 24, 10:00 A.M., Room No. 101, Exhibition Floor

Committee on Academic Regalia

Sunday, April 24, 11:00 A.M., Room No. 101, Exhibition Floor

Co-operative Committee with the Royal Colleges

Sunday, April 24, 12:00 M., Room No. 101, Exhibition Floor

Joint Meeting: Board of Regents and Board of Governors

Sunday, April 24, 2:00 P.M., Room No. 101, Exhibition Floor

Joint Meeting: (Reconvene) Board of Regents and Board of Governors

Monday, April 25, 10:00 A.M., Room No. 101, Exhibition Floor

Inspection, Committee on Technical Exhibits

Monday, April 25, 10:30 A.M., starting from the Executive Secretary's Office, Exhibition Floor

Meeting, Technical Exhibitors

Monday, April 25, 5:20 P.M., Room No. 101, Exhibition Floor

Meeting, Board of Governors

*Tuesday, April 26, 12:00 M., Room No. 101, Exhibition Floor

Meeting, Board of Regents

*Wednesday, April 27, 12:00 M., Room No. 101, Exhibition Floor

Annual Business Meeting

Thursday, April 28, 2:00 P.M., Auditorium, Convention Hall

Meeting, Board of Regents (Organization Meeting)

Friday, April 29, 9:00 A.M., Room No. 101, Exhibition Floor

SPECIAL FEATURES

Post-Convention Cruise to Nassau and Havana—A Post-Convention Cruise on the *SS Nassau* will leave New York on Friday night, April 29, arriving in Nassau on May 2 for a two-day stay and then proceed to Havana for arrival on May 4, leaving on May 7, and getting back to New York on May 9 in the morning. Ample time is available at the conclusion of the Philadelphia program to reach shipside before sailing. An interesting, though short, scientific program has been arranged aboard ship and at Havana, with an opportunity to visit the University of Havana Medical School and other points of medical interest. An especially attractive program of sight-seeing and shopping, in both Nassau and Havana, with special luncheons and dinners ashore, have been arranged.

An illustrated and detailed itinerary appeared in the December, 1954, Issue of the ANNALS OF INTERNAL MEDICINE. Post-Convention Cruises and Tours have often been arranged for the College in past years, and without exception, they have proved

* Buffet luncheon served.

to be particularly well arranged and conducted. Rates for this cruise vary from $300.00 to $400.00 per person, plus 10% Federal Tax and $3.85 local Port Taxes. Full information, itineraries, ship's plans and other details may be obtained from Mr. J. P. Sims, Jr., Raymond-Whitcomb, Inc., 1600 Walnut Street, Philadelphia 3, Pa. It is highly important to make reservations early, before the accommodations held by the College are exhausted.

Concert, The Philadelphia Orchestra, Monday evening, April 25, 8:30 P.M., Academy of Music, Broad and Locust Streets, Philadelphia—The Committee on Entertainment is gratified to announce a Concert by the great Philadelphia Orchestra, under the direction of Eugene Ormandy, who is planning a most attractive program for the College members. Citizens of Philadelphia and its environs are devoted to its great Orchestra, and it will be a special privilege to have this Orchestra entertain the members of the College at a private Concert. In view of the fact that there is no sponsoring agency this year, a small charge of $2.00 per ticket will be made to partially underwrite the cost. The Executive Office of the College will fill requests for tickets, first come, first served. Members should send in their applications immediately; non-members, duly registered at the Session, may obtain tickets at the A.C.P. Registration Desk at Convention Hall on Sunday afternoon, April 24, or Monday forenoon, April 25. The Academy of Music seats approximately 3,400. Seats will be reserved only for Officers, Regents, Governors, distinguished guests, and their wives. This concert will be one of the social highlights of the 36th Annual Session of the College.

Reception and Dinner, tendered by Governors of the College to new Associates and Direct Fellows: Bellevue-Stratford Hotel, North Garden and Rose Garden, 18th floor, Tuesday evening, April 26, 6:30 P.M.—The Governors of the College extend an invitation to all new Associates and Direct Fellows who have been elected on or since April 4, 1954, for the purpose of welcoming them to the College and to provide an opportunity to meet them personally and for them to meet the Officers and Regents of the College, as well as one another. Special invitations will be issued by mail in advance of the Annual Session. It is urgent that the Executive Office receive acceptances, or declinations, promptly and in advance.

The Annual Convocation and President's Reception: Bellevue-Stratford Hotel, Wednesday evening, April 27, 8:40 P.M.—The 1955 Annual Convocation of the College will take place in the Ballroom of the Bellevue-Stratford Hotel at time above designated. All members of the College and their families, and the Philadelphia public who are interested, are very cordially invited. Tickets will not be required. All physicians elected Fellows of the College since the 1954 Convocation, and all previously elected Fellows who have not been formally inducted, should be present. Officers, Regents, Governors, distinguished guests on the program, and new Fellows to be inducted are requested to assemble in the Clover Room, Ballroom Floor, at 8:00 P.M., preparatory to the formation of the Procession, which will move promptly at 8:40 o'clock.

The Convocation Ceremony will include the induction of new Fellows, a short charge to the new members by the President, Dr. Cyrus C. Sturgis, and the Convocational Oration, "Disorders of Contemporary Society and Their Impact on Medicine," by Dr. George W. Pickering, Professor of Medicine, University of London (England). The John Phillips Memorial Medal for 1955, the James D. Bruce Memorial Medal for 1955 and the Alfred Stengel Diploma for 1955 will be awarded. Masterships will be conferred upon three distinguished Fellows of the College and an Honorary Fellowship upon the guest speaker. Among other distinguished guests, there will be present the Presidents of the American College of Surgeons, the American Medical Association and the Royal College of Physicians and Surgeons of Canada.

Immediately following the Convocation the President's Reception will follow in the Clover Room, just outside the Ballroom. Dancing will start in the Ballroom about

10:30 P.M., continuing to 1:00 A.M. Tables for individual parties will be available beneath the balcony, around the periphery of the dance floor.

The Annual Banquet: Benjamin Franklin Hotel, Ballroom, Mezzanine Floor, Thursday, April 28, 8:00 P.M.—At 7:00 P.M., in the Betsy Ross and Franklin Rooms, Mezzanine Floor of the Benjamin Franklin Hotel, will be held a "Dutch Treat" Cocktail Party, to which all members and their guests are cordially invited.

The Annual Banquet will follow at 8:00 o'clock in the Ballroom. Mr. Ogden Nash, internationally noted author and speaker, will be the Speaker of the Day. The Temple University Concert Choir, of nationwide renown, conducted by Mrs. Elaine Brown, will provide special entertainment. The Entertainment Committee has planned a gala occasion, and it is confidently expected that a large proportion of the members and guests, with their ladies, will be in attendance. Table reservations for groups of ten may be arranged in advance. Tickets should be procured at the Registration Bureau on the Exhibition Floor of Convention Hall by 2:00 P.M., Wednesday, April 27, in order that adequate preparations may be concluded by the Committee.

ENTERTAINMENT OF VISITING WOMEN

The Committee on Ladies' Entertainment in Philadelphia presents the following program of entertainment and extends a cordial invitation to the wives and daughters of College members to register and to participate.

Certain of the entertainment features are limited in accommodations; the Committee must make guarantees in advance in several cases; therefore, your co-operation and early registration is urged. Every effort will be made to fill reservations in the order of receipt. Tickets not called for before the deadlines indicated will be released. It will help the Committee if you will return your reservation cards by March 25, and thereafter to send prompt notice of any change of plans.

Headquarters for the Ladies' Registration will be in the Betsy Ross Room, Mezzanine Floor, Benjamin Franklin Hotel. There you will purchase your tickets for featured events; and there, too, you will find restful chairs and a convenient meeting place for you and your friends.

Registration Hours

(Betsy Ross Room, Benjamin Franklin Hotel)

Sunday	2:00 P.M. to 5:00 P.M.
Monday	9:00 A.M. to 4:00 P.M.
Tuesday	9:00 A.M. to 4:00 P.M.
Wednesday	9:00 A.M. to 4:00 P.M.
Thursday	9:00 A.M. to 12:30 P.M.

Ladies' Program

Monday, April 25

"WELCOME DAY"; coffee will be served in the morning and afternoon; wives of Regents, Governors and ladies on the Entertainment Committee will serve as hostesses.

8:30 P.M. Concert by the Philadelphia Orchestra, Academy of Music.

Tuesday, April 26

Trip to Winterthur Museum, Wilmington, Del. Busses will leave the hotel at approximately 10:30 A.M. Luncheon will be served in the Court Yard of the Museum.

As an alternate for the above, the Baltimore & Ohio Railroad is offering a most attractive all-day conducted excursion to Washington, D. C., providing for a visit to the White House, luncheon at the new Statler Hotel, visits to the Washington

Monument, Smithsonian Buildings, National Gallery of Art, Department of Commerce, Internal Revenue, F.B.I., United States Capitol, Jefferson Memorial, and other places of special interest.

Leave Baltimore & Ohio Railroad Station, 24th and Chestnut Streets, 8:00 A.M.; arrive Washington, 10:45 A.M.; leave Washington, 3:45 P.M.; arrive Philadelphia, 6:00 P.M. Price, including round trip transportation, tax, sight-seeing admissions, guides and luncheon, $14.25.

Wednesday, April 27

2:00 P.M. Fashion Show and Tea at The John Wanamaker Store.

8:40 P.M. The Annual Convocation, followed by the President's Reception and Ball, in the Grand Ballroom of the Bellevue-Stratford Hotel. Ladies are cordially invited; no charge.

Thursday, April 28

12:00 M. Luncheon at Franklin Institute; 1:00 P.M., lecture and show at the Planetarium; 2:15 P.M., tour of Fairmount Park to visit two of the old Colonial Houses.

7:00 P.M. Cocktail Party, followed by the Annual Banquet at 8:00 P.M. in the Grand Ballroom of the Bellevue-Stratford Hotel.

An appropriate charge, at cost, will be made for each event.

At the Ladies' Headquarters will be available information about all points of interest in Philadelphia, sight-seeing tours, visits to museums, shops, restaurants, etc.

Color Televised Clinics—Again through the courtesy of Smith, Kline & French Laboratories, Philadelphia, and the co-operation of Columbia Broadcasting System, the College will present for the sixth year an interesting program of clinics televised in color from the Mills Building of the Philadelphia General Hospital to Convention Hall, Exhibition Floor, from 9:00 A.M. to 11:00 A.M., daily, Tuesday through Friday, April 26–29, inclusive.

A technical feature of the television program will be the use of the greatly magnified color pictures, produced by two projection-type receivers equipped with large screens, 4½ feet by 6 feet, which furnish a picture 27 times larger than the small screens formerly used. These larger screens were first introduced before the College meeting in 1954 and produced markedly better results, attracting a considerably larger audience. The role color television is playing in scientific teaching programs is a pointed indication of an ever growing importance of this vehicle in medical education.

"Medical Films That Teach"—The Medical Film Guild, of New York City, again will present several timely, new films, produced in color and sound, during the meeting. They will be located in Booth No. 31 in the Technical Exhibit and special showings will be made in the General Sessions Hall (Auditorium) on the afternoons of Monday, Tuesday, Wednesday and Thursday. Showings will be announced and posted on the Bulletin Board. Among the new films will be "Pitfalls of Congestive Failure," a thirty-five minute film; format will show rounds in the Heart Clinic at Georgetown University, with flashbacks to the laboratory, supplemented by physiological discussion; "Ocular Bacteriology," its application to clinical practice; produced at Tulane University of Louisiana School of Medicine, and while not too closely allied with Internal Medicine, it represents an object lesson of how to treat medical problems; a panel discussion, with flashbacks to the Clinic and Research Laboratory.

Clinical-Pathological Conferences—Case presentations will be distributed in advance to all members of the College and its guests. These will be discussed by the clinicians who are expected to make the correct diagnoses, and, perhaps, to criticize the treatment. The postmortem findings, their interpretation and their integration with the clinical aspects will then be presented by the pathologist. Moderators and conference personnel will answer questions as time permits. These conferences appear

on the program daily, from 11:40 A.M. to 1:00 P.M., Tuesday through Friday, with two special cases on Friday afternoon.

Clinical-Physiological Conference—An entirely new introduction to the program of the College, Wednesday, April 27, 11:40 A.M. to 1:00 P.M.

The Technical Exhibit will be located on the Exhibition Floor of Convention Hall, and will be an outstanding example of the ever improving technical exhibits of the College. More than 100 firms have subscribed for 136 exhibit booths. Their exhibits will cover the wide range of interest of internists and allied specialists everywhere.

The Committee on Exhibits maintains high standards in the conduct of this Exhibit. Exhibitors are admitted only by invitation. Irrelevant exhibits are eliminated, and only firms which present a group of approved products or services of scientific interest to the internist and allied specialist may exhibit.

Exhibits will be open from 8:45 A.M. to 5:30 P.M., daily, Monday through Thursday, and from 8:45 A.M. to 12:45 P.M. on Friday. The Technical Exhibitors gauge the meeting by the amount of interest shown and the co-operation displayed by the College. Members and guests are encouraged to accord the exhibitors courteous and interested attention. The exhibits constitute a real educational program in connection with the Annual Session.

PARTIAL LIST OF TECHNICAL EXHIBITORS

	Booth
Abbott Laboratories, North Chicago, Ill.	93–94
Alkalol Company, The, Taunton, Mass.	16
American Ferment Co., Inc., New York, N. Y.	120
American Hospital Supply Corporation, Evanston, Ill.	116
Ames Company, Inc., Elkhart, Ind.	53
Appleton-Century-Crofts, Inc., New York, N. Y.	26
Armour Laboratories, The, Kankakee, Ill.	40
Association of American University Presses, New Haven, Conn.	44
Audio-Digest Foundation, Glendale, Calif.	29
Ayerst Laboratories, New York, N.Y.	85–86
W. A. Baum Co., Inc., Copiague, L. I., N. Y.	45
Becton, Dickinson and Company, Rutherford, N. J.	136
J. Beeber Company, Inc., New York, N. Y.	129
Bilhuber-Knoll Corp., Orange, N. J.	95
Blakiston Division, McGraw-Hill Book Co., Inc., New York, N. Y.	23
Borcherdt Malt Extract Company, Chicago, Ill.	122
Borden Company, The, New York, N. Y.	8
Bowen & Company, Inc., Bethesda, Md.	132
Brewer & Company, Inc., Worcester, Mass.	32
Burdick Corporation, The, Milton, Wis.	115
Burroughs Wellcome & Co. (U.S.A.) Inc., Tuckahoe, N. Y.	105
Burton, Parsons & Company, Washington, D. C.	133
Cambridge Instrument Co., Inc., New York, N. Y.	22
Carnation Company, Los Angeles, Calif.	100
Chilean Iodine Educational Bureau, Inc., New York, N. Y.	124
Ciba Pharmaceutical Products, Inc., Summit, N. J.	63–64
Warren E. Collins, Inc., Boston, Mass.	72
County Surgical Co., Inc., Brooklyn, N. Y.	121

	Booth
Davies, Rose & Company, Limited, Boston, Mass.	17
F. A. Davis Company, Philadelphia, Pa.	49
Desitin Chemical Company, Providence, R. I.	108
Devereux Schools, Devon, Pa.	130
DeVilbiss Company, The, Somerset, Pa.	48
Doho Chemical Corporation, New York, N. Y.	87–88
Duke Laboratories, Inc., Stamford, Conn.	102
Eaton Laboratories, Norwich, N. Y.	9
Edin Company, Inc., Worcester, Mass.	36
Electro-Physical Laboratories, Inc., Boston, Mass.	109
Fellows Medical Mfg. Co., Inc., New York, N. Y.	43
Fine Chemicals Division, American Cyanamid Company, New York, N. Y.	20–21
C. B. Fleet Co., Inc., Lynchburg, Va.	66
Geigy Pharmaceuticals, Division of Geigy Chemical Corporation, New York, N. Y.	4
General Electric Company, X-Ray Department, Milwaukee, Wis.	2–3
General Foods Corporation, White Plains, N. Y.	68–69, 74–75–76
Gerber Products Company, Fremont, Mich.	62
Grune & Stratton, Inc., New York, N. Y.	98
H. J. Heinz Company, Pittsburgh, Pa.	106
Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York, N. Y.	1
Hoffmann-La Roche Inc., Nutley, N. J.	65
Hollister-Stier Laboratories, Philadelphia, Pa.	7
Horlicks Corporation, Pharmaceutical Division, Racine, Wis.	119
Hospital Bedhite Company, Fort Worth, Tex.	18
Hyland Laboratories, Los Angeles, Calif.	114
Irwin, Neisler & Company, Decatur, Ill.	47
Ives-Cameron Company, Philadelphia, Pa.	103
Jones Metabolism Equipment Co., Inc., Chicago, Ill.	123
"Junket" Brand Foods, Little Falls, N. Y.	55
Lea & Febiger, Philadelphia, Pa.	71
Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.	27
Liebel-Flarsheim Company, The, Cincinnati, Ohio	11
Eli Lilly and Company, Indianapolis, Ind.	111–112–113
J. B. Lippincott Company, Philadelphia, Pa.	56
Little, Brown & Company, Boston, Mass.	135
Lloyd Brothers, Inc., Cincinnati, Ohio	35
Macmillan Company, The, New York, N. Y.	52
Massachusetts Indemnity Insurance Company, Boston, Mass.	10
Mead Johnson & Company, Evansville, Ind.	39
Medco Products Company, Tulsa, Okla.	28
Medical Bureau, The, Chicago, Ill.	70
Medical Case History Bureau, New York, N. Y.	24

	Booth
Medical Film Guild, Ltd., New York, N. Y.	31
Merck & Co., Inc., Rahway, N. J.	57–58
Wm. S. Merrell Company, The, Cincinnati, Ohio	127–128
C. V. Mosby Company, The, St. Louis, Mo.	73
National Drug Company, The, Philadelphia, Pa.	50–51
Nepera Chemical Co., Inc., Yonkers, N. Y.	81
Parke, Davis & Company, Detroit, Mich.	15
Pet Milk Company, St. Louis, Mo.	13
Pfizer Laboratories, Brooklyn, N. Y.	5–6
W. F. Prior Company, Inc., Hagerstown, Md.	33
Riker Laboratories, Inc., Los Angeles, Calif.	107
A. H. Robins Company, Inc., Richmond, Va.	99
J. B. Roerig and Company, Chicago, Ill.	54
Sanborn Company, Cambridge, Mass.	117–118
Sandoz Chemical Works, Inc., Pharmaceutical Division, New York, N. Y.	96
W. B. Saunders Company, Philadelphia, Pa.	41–42
Schenley Laboratories, Inc., New York, N. Y.	14
Schering Corporation, Bloomfield, N. J.	38
Schieffelin & Co., New York, N. Y.	101
G. D. Searle & Co., Chicago, Ill.	131
Sharp & Dohme, Division of Merck & Co., Inc., Philadelphia, Pa.	59–60–61
Smith, Kline & French Laboratories, Philadelphia, Pa.	83–84
E. R. Squibb & Sons, Division of Mathieson Chemical Corporation, New York, N. Y.	89–90
S. J. Tutag & Company, Detroit, Mich.	34
Upjohn Company, The, Kalamazoo, Mich.	79–80
U. S. Vitamin Corporation, New York, N. Y.	97
Varick Pharmacal Company, Inc., Division of E. Fougera & Co., Inc., New York, N. Y.	104
Wallace & Tiernan Incorporated, Belleville, N. J.	67
Warner-Chilcott Laboratories, New York, N. Y.	134
White Laboratories, Inc., Kenilworth, N. J.	82
Williams & Wilkins Company, The, Baltimore, Md.	46
Winthrop-Stearns Inc., New York, N. Y.	77–78
Woodward Medical Personnel Bureau, Chicago, Ill.	25
Wyeth Laboratories, Philadelphia, Pa.	91–92
Year Book Publishers, Inc., The, Chicago, Ill.	110
Yorke Publishing Company, Inc., The, New York, N. Y.	37

Additionally, special exhibits will be set up by the Armed Forces Institute of Pathology, the Bureau of Medicine and Surgery of the Department of the Navy, and The National Foundation for Infantile Paralysis.

OUTLINE OF THE PHILADELPHIA SESSION
(Bold type indicates programs at Convention Hall)

TIME	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY
	April 25	April 26	April 27	April 28	April 29
9:00 A.M. to 11:00 A.M.	Morning free **Registration, Exhibits, etc.**	*Hospital Clinics **Lectures and Symposia Color Televised Clinics**	**Lectures and Symposia Color Televised Clinics**	*Hospital Clinics **Lectures and Symposia Color Televised Clinics**	**Lectures and Symposia Color Televised Clinics**
11:00 A.M. to 11:40 A.M.		**Intermission**	**Intermission**	**Intermission**	**Intermission**
11:40 A.M. to 1:00 P.M.		**Panels C-P Conferences**	**Panels Clinical-Physiological Conference**	**Panels C-P Conferences**	**Panels C-P Conferences**
2:00 P.M. to 3:00 P.M.	**1st General Session**	**2nd General Session**	**3rd General Session**	**Annual Business Meeting 4th General Session**	**5th General Session**
3:00 P.M. to 3:40 P.M.	**Intermission**	**Intermission**	**Intermission**	**Intermission**	**3:30 P.M. to 5:00 P.M. C.P.C.'s (2)**
3:40 P.M. to 5:00 P.M.	**1st General Session** (Continued)	**2nd General Session** (Continued)	**3rd General Session** (Continued)	**4th General Session** (Continued)	
5:00 P.M. to 5:30 P.M.	**Exhibits**	**Exhibits**	**Exhibits**	**Exhibits**	
Evening	Symphony Concert	Reception to New Members	Convocation and President's Reception	Annual Banquet	

* Some at Convention Hall; some at near-by hospitals.

CAMDEN, N. J.
CONVENTION HALL
HOTELS (indicated by numbers on map)
HOSPITALS (indicated by letters)
CHILDREN'S, 19th & Bainbridge Sts. ——— A
GRADUATE, 20th & Lombard Sts. ——— B
HAHNEMANN, Broad & Race Sts. ——— C
UNIVERSITY, 34th & Spruce Sts. ——— D
JEFFERSON, 10th & Sansom Sts. ——— E
LANKENAU, Lancaster Ave. beyond City Line ——— F
PENNSYLVANIA, 9th & Spruce Sts. ——— G
PHILADELPHIA GENERAL, Curtis Below 34th ——— H
POLYCLINIC, 17th & Lombard Sts. ——— I
VETERANS, University & Woodland Aves. ——— J
(Other hospitals will conduct their clinics at Convention Hall or Philadelphia General Hospital)

GENERAL SESSIONS PROGRAM

Auditorium, Convention Hall

FIRST GENERAL SESSION

Monday Afternoon, April 25, 1955

Presiding Officer

THOMAS M. DURANT, F.A.C.P., Philadelphia,
General Chairman

P.M.

2:00 Invocation:
The Reverend DONALD GREY BARNHOUSE, Th.M., D.D., Minister, Tenth Presbyterian Church of Philadelphia; Legion of Honor (France).

Address of Welcome:
The Honorable JOSEPH S. CLARK, JR., Mayor of the City of Philadelphia.

Response to Address of Welcome:
CYRUS C. STURGIS, F.A.C.P., President, The American College of Physicians.

Presiding Officer

President CYRUS C. STURGIS, F.A.C.P., Ann Arbor

2:20 The James D. Bruce Memorial Lecture on Preventive Medicine: Antibiotic Products of a Versatile Fungus.
SIR HOWARD WALTER FLOREY, F.R.C.P., F.R.S., M.D., Ph.D., (by invitation), Professor of Pathology, Sir William Dunn School of Pathology, University of Oxford, Oxford, England.

2:45 The Practical Etiology of Atherosclerosis.
ANCEL KEYS, Ph.D., (by invitation), Professor and Director, Laboratory of Physiological Hygiene, School of Public Health, University of Minnesota, Minneapolis.

3:05 The Clinical Value of Kidney Biopsy.
ROBERT M. KARK, F.A.C.P., Professor of Medicine, ROBERT C. MUEHRCKE, M.D., (by invitation), Assistant in Medicine, and CONRAD L. PIRANI, M.D., (by invitation), Associate Professor of Pathology; University of Illinois College of Medicine, Chicago.

3:25 INTERMISSION.

4:05 The Clinical Significance of the Low Salt Syndrome.
T. S. DANOWSKI, F.A.C.P., Professor of Research Medicine, University of Pittsburgh School of Medicine, Pittsburgh.

4:25 Aldosterone: Observations on the Regulation of Sodium Balance.
JOHN A. LUETSCHER, JR., M.D., (by invitation), Associate Professor of Medicine, Stanford University School of Medicine, San Francisco.

4:45 Symptomatology and Treatment of Hiatus Hernia.
CHESTER M. JONES, F.A.C.P., Clinical Professor of Medicine, Harvard Medical School; Consulting Physician, Massachusetts General Hospital; Boston.

5:05 ADJOURNMENT.

5:05 Elective: "Pitfalls of Congestive Failure."

A motion picture film in color and sound—35 minutes. From the Heart Clinic of Georgetown University Hospital; bedside discussions about pitfalls in therapy; flashbacks to the Laboratory, supplemented by physiologic discussion.

SECOND GENERAL SESSION

Auditorium, Convention Hall

Tuesday Afternoon, April 26, 1955

Presiding Officer

WALTER L. PALMER, F.A.C.P., Chicago

P.M.

2:00 The Genetic Factor in Essential Hypertension.

GEORGE W. PICKERING, M.A., M.B. (Cantab.), F.R.C.P., M.D. (H.C. Ghent), (by invitation), Professor of Medicine, University of London; Director, Medical Clinic, St. Mary's Hospital Medical School; London, England.

2:25 The Present Status of the Treatment of Incapacitated Euthyroid Cardiac Patients with Radioactive Iodine.

HERRMAN L. BLUMGART, F.A.C.P., Professor of Medicine, Harvard Medical School; Physician-in-Chief, Beth Israel Hospital; Boston.

2:45 Certain Factors Affecting the Long-Term Results in the Operative Treatment of Mitral Stenosis.

LAURENCE B. ELLIS, F.A.C.P., Associate Clinical Professor of Medicine, Harvard Medical School; Director, Cardiac Clinic, Boston City Hospital; Boston.

3:05 On the Choice of Treatment for Hyperthyroidism.

E. PERRY MCCULLAGH, F.A.C.P., Head of Section of Endocrinology and Metabolism, Cleveland Clinic, Cleveland.

3:25 INTERMISSION.

4:05 Nodular Goiter: The Indications for Medical and Surgical Therapies.

OLIVER COPE, M.D., (by invitation), Associate Professor of Surgery, Harvard Medical School; Visiting Surgeon, Massachusetts General Hospital; Boston.

4:25 The Hepatitis Problem.

JOHN R. NEEFE, F.A.C.P., Associate in Medicine, University of Pennsylvania School of Medicine; Associate, Pepper Laboratory of Clinical Medicine, Hospital of the University of Pennsylvania; Philadelphia.

4:45 Virus Inactivation in Plasma—An Approach in the Control of Serum Hepatitis.

FRANK W. HARTMAN, M.D., (by invitation), Pathologist-in-Chief, Henry Ford Hospital, Detroit.

5:05 ADJOURNMENT.

5:05 Elective: "Ocular Bacteriology."

A motion picture in color and sound—40 minutes. From Tulane University of Louisiana School of Medicine; format of film is a panel discussion, with flashbacks to the Clinic and Research Laboratory.

THIRD GENERAL SESSION

Auditorium, Convention Hall

Wednesday Afternoon, April 27, 1955

Presiding Officer

WALLACE M. YATER, F.A.C.P., Washington

P.M.

1:45 **The President's Report.**
CYRUS C. STURGIS, F.A.C.P., Ann Arbor.

2:00 **The John Phillips Memorial Lecture: Studies on Fluorohydrocortisone and Aldosterone.**
GEORGE W. THORN, F.A.C.P., Hersey Professor of the Theory and Practice of Physic, Harvard Medical School, Boston.

2:25 **Primary Aldosteronism, A New Clinical Syndrome.**
JEROME W. CONN, F.A.C.P., Professor of Internal Medicine, University of Michigan Medical School, Ann Arbor.

2:45 **Clinical Aspects of Plasma Volume Expansion.**
WALTER LYON BLOOM, M.D., (by invitation), Assistant Professor of Medicine and Assistant Professor of Biochemistry, Emory University School of Medicine, Atlanta.

3:05 INTERMISSION.

3:45 **The Preservation of Blood for Transfusion Purposes.**
CLEMENT A. FINCH, M.D., (by invitation), Associate Professor of Medicine, University of Washington School of Medicine, Seattle.

4:05 **New Developments in the Diagnosis and Treatment of Pernicious Anemia.**
C. LOCKARD CONLEY, M.D., (by invitation), Associate Professor of Medicine, Johns Hopkins University School of Medicine, Baltimore.

4:25 **Epidemiologic Considerations of Sarcoidosis.**
MAX MICHAEL, JR., M.D., (by invitation), Professor of Medicine, State University of New York College of Medicine at New York City; Director of Medical Services, Maimonides Hospital of Brooklyn; JOHN T. GENTRY, M.D., (by invitation), District State Health Officer, Syracuse, and HAROLD M. NITOWSKY, M.D., (by invitation), Assistant Chief Pediatrician, Sinai Hospital, Baltimore.

4:45 **The Diagnosis of Sarcoidosis with Special Reference to the Kveim Reaction.**
HAROLD L. ISRAEL, F.A.C.P., Associate Professor of Medicine, University of Pennsylvania Graduate School of Medicine, and MAURICE SONES, F.A.C.P., Assistant Professor of Medicine, Woman's Medical College of Pennsylvania; Philadelphia.

5:05 ADJOURNMENT.

ANNUAL CONVOCATION

Wednesday Evening, April 27, 1955

8:40 o'Clock

Grand Ballroom, Bellevue-Stratford Hotel

LEMUEL C. McGEE, Marshal

Pre-Convocation Assembly of Fellows to be inducted, Officers, Regents, Governors, Distinguished Guests and Recipients of Awards, Clover Room, Bellevue-Stratford Hotel, Ballroom Floor, at 8:00 P.M.

All members of the profession and the general public are cordially invited.

1. Processional.
2. The President's Charge to New Fellows of the American College of Physicians.
   CYRUS CRESSEY STURGIS.
3. Conferring of Fellowships by the President.
4. Conferring of Masterships by the President.
5. Conferring of Honorary Fellowship by the President.
6. Presentation of the John Phillips Memorial Medal for 1955.
7. Presentation of the James D. Bruce Memorial Medal for 1955.
8. Presentation of the Alfred Stengel Memorial Award for 1955.
9. Convocation Oration: "Disorders of Contemporary Society and Their Impact on Medicine."
   GEORGE W. PICKERING, F.R.C.P., Professor of Medicine, University of London.
10. Recessional.

The President's Reception and Ball will follow at 10:15 o'clock. The audience is requested to vacate the Grand Ballroom temporarily while the room is reset for Dancing. A cordial invitation is extended to all members and guests, with their families.

FOURTH GENERAL SESSION

Auditorium, Convention Hall

Thursday Afternoon, April 28, 1955

P.M.

2:00 THE ANNUAL BUSINESS MEETING.

All Fellows and Masters are urged to be present and to participate more actively in the administrative problems of the College. Announcements will be made of the Research Fellowship Awards, Latin-American Fellowship Awards, the A. Blaine Brower Traveling Scholarship Awards, the Elizabeth Archbold Bowes Traveling Scholarship Award and the Mead Johnson Postgraduate Scholarship Awards. Reports will be received from the Secretary-General, Executive Secretary and Treasurer; elections of new Officers, Regents and Governors will take place; President-Elect George F. Strong, of Vancouver, B. C., will be inducted as President and will make a brief inaugural address.

Presiding Officer

CARTER SMITH, F.A.C.P., Atlanta

2:40 **The Lilly Lecture: Three Types of Human Diabetes.**
ROBERT D. LAWRENCE, F.R.C.P., (by invitation), Physician-in-Charge, Diabetic Department, King's College Hospital, London, England.

3:05 **Can the Practice of Internal Medicine be Evaluated?**
C. WESLEY EISELE, F.A.C.P., Associate Professor of Medicine, and Director of Postgraduate Medical Education, University of Colorado School of Medicine, Denver; VERGIL N. SLEE, M.D., (by invitation), Director of the Professional Activity Study of the Southwestern Michigan Hospital Council, Hastings, and ROBERT G. HOFFMANN, Ph.D., (by invitation), Statistician for the Professional Activity Study for the Southwestern Michigan Hospital Council, Ann Arbor.

3:25 INTERMISSION.

4:05 **Defective Serum Gamma Globulin Formation.**
THOMAS H. BREM, (Associate), Professor of Medicine, University of Southern California School of Medicine, and M. E. MORTON, M.D., (by invitation), Associate Clinical Professor of Biophysics and Clinical Instructor in Medicine, University of California School of Medicine; Chief of Radioisotope Division, Veterans Administration Hospital (Long Beach); Los Angeles.

4:25 **Comparative Evaluation of the L. E. Tests.**
JOHN R. HASERICK, F.A.C.P., Department of Dermatology, Cleveland Clinic Foundation, Cleveland.

4:45 **Evaluation of Present Day Methods of Treating Rheumatoid Arthritis.**
JOSEPH J. BUNIM, F.A.C.P., Clinical Director, National Institute of Arthritis and Metabolic Diseases, Bethesda.

5:05 ADJOURNMENT.

Thursday Evening, April 28, 1955

7:00 o'Clock

Betsy Ross and Franklin Rooms, Mezzanine Floor, Benjamin Franklin Hotel

"DUTCH TREAT" COCKTAIL PARTY

8:00 o'Clock

Ballroom, Mezzanine Floor, Benjamin Franklin Hotel

THE ANNUAL BANQUET OF THE COLLEGE

Toastmaster:

THOMAS M. DURANT, F.A.C.P., Philadelphia

Address of the Day:

"Midway Thru Nash"

OGDEN NASH, Internationally Known Humorist, Author and Speaker

Procure tickets at the Registration Bureau, Exhibition Floor, Convention Hall, before 2:00 P.M., Wednesday. Arrangements may be made for table reservations.

FIFTH GENERAL SESSION

Auditorium, Convention Hall

Friday Afternoon, April 29, 1955

Presiding Officer

J. MURRAY KINSMAN, F.A.C.P., Louisville

P.M.

2:00 The Problem of Peptic Ulcer.

F. AVERY JONES, F.R.C.P., (by invitation), Physician-in-Charge, Gastroenterological Unit, Central Middlesex Hospital; Consultant in Gastroenterology, Postgraduate Medical School of London, St. Mark's Hospital, and Royal Navy; London, England.

2:25 The Physiological Diagnosis and Treatment of Chronic Emphysema.

JULIUS H. COMROE, JR., F.A.C.P., Professor of Physiology and Pharmacology, University of Pennsylvania Graduate School of Medicine, Philadelphia.

2:45 The Need for More Details in Cancer Data.

STANLEY P. REIMANN, F.A.C.P., Professor of Oncology, Hahnemann Medical College and Hospital of Philadelphia; Associate Professor of Surgical Pathology, University of Pennsylvania Graduate School of Medicine; Director of Research Institute, Lankenau Hospital; Scientific Director, Institute for Cancer Research; Philadelphia.

3:05 Evaluation of the Present Day Treatment of Pulmonary Tuberculosis.

J. BURNS AMBERSON, F.A.C.P., Professor of Medicine, Columbia University College of Physicians and Surgeons, New York.

3:25 ADJOURNMENT, followed by two Clinical-Pathological Conferences.

Auditorium, Convention Hall

3:30 CASE NO. 1:

Moderator

O. H. PERRY PEPPER, M.A.C.P.
Philadelphia

Clinicians

SOL KATZ, F.A.C.P.
Washington

CLEMENT A. FINCH
Seattle

JOHN E. DEITRICK, F.A.C.P.
Philadelphia

Pathologist

W. A. D. ANDERSON, F.A.C.P.
Coral Gables

4:15 CASE NO. 2:

Moderator
O. H. PERRY PEPPER, M.A.C.P.
Philadelphia

Clinicians
CHARLES L. BROWN, F.A.C.P.
Philadelphia
J. RUSSELL ELKINTON, F.A.C.P.
Philadelphia
HENRY M. THOMAS, JR., F.A.C.P.
Baltimore

Pathologist
PETER A. HERBUT, F.A.C.P.
Philadelphia

5:00 ADJOURNMENT

MORNING LECTURES AND SYMPOSIA

There are one Symposium on Tuesday morning, two Lectures and one Symposium on Wednesday morning and one Symposium on Thursday morning and two Symposia on Friday morning.

Admission by regular registration badge; no special tickets required.

Tuesday, April 26, 1955

I. SYMPOSIUM ON ACUTE MYOCARDIAL INFARCTION

Auditorium, Convention Hall

Presiding Officer
GEORGE F. STRONG, F.A.C.P., Vancouver

A.M.

9:00 **The Role of Diet and Hormones in the Prevention of Myocardial Infarction.**
LOUIS N. KATZ, F.A.C.P., Professorial Lecturer in Physiology, University of Chicago School of Medicine; Director, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital; Chicago.

9:25 **A Critical Evaluation of the Value of the Electrocardiogram in the Diagnosis of Myocardial Infarction.**
FRANKLIN D. JOHNSTON, F.A.C.P., Professor of Internal Medicine, University of Michigan Medical School, Ann Arbor.

9:50 **Chair Rest versus Bed Rest, and Ambulation in the Treatment of Myocardial Infarction.**
SAMUEL A. LEVINE, F.A.C.P., Clinical Professor of Medicine, Harvard Medical School; Physician, Peter Bent Brigham Hospital; Boston.

10:15 **The Present Status of Anticoagulant Therapy, Its Use and Misuse; New Anticoagulants, Their Advantages and Disadvantages and Dosage.**
IRVING S. WRIGHT, F.A.C.P., Professor of Clinical Medicine, Cornell University Medical College; Attending Physician, New York Hospital; New York.

10:45 The Control of Excessive Effect by Anticoagulants.
IVAN F. DUFF, (Associate), Associate Professor of Internal Medicine, University of Michigan Medical School, Ann Arbor.

11:00 ADJOURNMENT, followed by Panel Discussions and Clinical-Pathological Conferences (Consult Panel Program).

Wednesday, April 27, 1955

II. SYMPOSIUM ON HYPERTENSION

Auditorium, Convention Hall

Presiding Officer

KARVER L. PUESTOW, F.A.C.P., Madison

A.M.

9:00 The Concept of Essential Hypertension.
GEORGE W. PICKERING, F.R.C.P., (by invitation), Professor of Medicine, University of London; Director, Medical Clinic, St. Mary's Hospital Medical School; London, England.

9:30 Evaluation of Antihypertensive Drugs.
A. C. CORCORAN, M.D., (by invitation), Assistant Director of Research, Cleveland Clinic Foundation, Cleveland.

10:00 Hypertension Treated by Nephrectomy.
GEORGE A. PERERA, M.D., (by invitation), Associate Professor of Medicine, Columbia University College of Physicians and Surgeons, New York.

10:20 The Value of Certain Tests Used Routinely in the Diagnosis of Pheochromocytoma in Patients with Hypertension.
EDWARD S. ORGAIN, F.A.C.P., Professor of Medicine, Duke University School of Medicine, Durham.

10:40 Evaluation of Sympathectomy in the Treatment of Hypertensive Disease.
S. W. HOOBLER, F.A.C.P., Associate Professor of Internal Medicine, University of Michigan Medical School, Ann Arbor.

11:00 ADJOURNMENT, followed by Panel Discussions and a Clinical-Physiological Conference (Consult Panel Program).

Wednesday, April 27, 1955

III. MORNING LECTURES

Ballroom, Third Floor, Convention Hall

Presiding Officer

H. MARVIN POLLARD, F.A.C.P., Ann Arbor

A.M.

9:00 Some Observations on Hematemesis and Melena.
F. AVERY JONES, F.R.C.P., (by invitation), Physician-in-Charge, Gastroenterological Unit, Central Middlesex Hospital; Consultant in Gastroenterology, Postgraduate Medical School of London, St. Mark's Hospital, and Royal Navy; London, England.

9:30 Mucoviscidosis, Current Concepts.
HARRY SHWACHMAN, M.D., (by invitation), Assistant Professor of Pediatrics, Harvard Medical School; Chief, Division of Clinical Laboratories, and Chief, Chronic Nutrition Clinic, Children's Medical Center; Boston.

9:45 **Guides to the Use of Cortisone and Hydrocortisone in Allergy.**
WALTER S. BURRAGE, F.A.C.P., Instructor in Medicine, Harvard Medical School; Associate Physician, Massachusetts General Hospital; Chief Consultant in Allergy, Veterans Administration, and JOHN W. IRWIN, M.D., (by invitation), Clinical and Research Fellow in Medicine, Massachusetts General Hospital; Boston.

10:00 **The Expanding Scope of Cardiovascular Radiology.**
MELVIN M. FIGLEY, M.D., (by invitation), Assistant Professor of Radiology, University of Michigan Medical School, Ann Arbor.

10:15 **The Value of Radioactive Iodine Uptake and Protein-Bound Iodine Estimations in the Diagnosis of Thyrotoxicosis.**
WILLIAM H. BEIERWALTES, F.A.C.P., Associate Professor of Internal Medicine, University of Michigan Medical School, Ann Arbor.

10:35 **The Treatment of Chronic Alcoholism; A Survey of Current Methods.**
DANIEL J. FELDMAN, F.A.C.P., Clinical Instructor in Medicine, New York University College of Medicine, New York.

11:00 ADJOURNMENT, followed by Panel Discussions and a Clinical-Physiological Conference (Consult Panel Program).

Wednesday, April 27, 1955

IV. MORNING LECTURES

Center Building, East, Exhibition Floor, Convention Hall

Presiding Officer

EUGENE B. FERRIS, F.A.C.P., Atlanta

A.M.

9:00 **Studies of Cholesterol Synthesis in Man, Using Carbon-14 Labeled Acetate.**
GEORGE V. LEROY, M.D., (by invitation), Associate Professor of Medicine, University of Chicago School of Medicine, Chicago.

9:20 **Potassium and the Kidney.**
WILLIAM B. SCHWARTZ, M.D., (by invitation), Assistant Professor of Medicine, Tufts College Medical School, Boston.

9:35 **Use of the External Electric Pacemaker in Cardiac Arrest.**
PAUL M. ZOLL, M.D., (by invitation), Assistant Professor of Medicine, Harvard Medical School; Visiting Physician, Head of Cardiac Clinic, and Associate in Medical Research, Beth Israel Hospital; Boston.

9:50 **The Transfer in Humans of Delayed Skin Sensitivity to Streptococcal M Substance and to Tuberculin with Components of Disrupted Leukocytes.**
H. SHERWOOD LAWRENCE, (Associate), Assistant Professor of Medicine, New York University College of Medicine, New York.

10:05 **The Intravenous Infusion of Bovine Crystalline Pancreatic Desoxyribonuclease in Patients.**
ALAN J. JOHNSON, M.D., (by invitation), Assistant Professor of Medicine, New York University College of Medicine, New York.

10:20 **Fructose Metabolism in Diabetes.**
MAX MILLER, M.D., (by invitation), Associate Professor of Medicine, Western Reserve University School of Medicine, Cleveland.

10:40 Serum Glutamic Oxalacetic Transaminase in the Detection and Evaluation of Acute Myocardial Infarction.

JOHN S. LADUE, F.A.C.P., Assistant Clinical Professor of Medicine, Cornell University Medical College; Associate Attending Physician, Memorial Hospital, and FELIX WROBLEWSKI, (Associate), Instructor in Medicine, Cornell University Medical College; New York.

11:00 ADJOURNMENT, followed by Panel Discussions and a Clinical-Physiological Conference (Consult Panel Program).

Thursday, April 28, 1955

V. SYMPOSIUM ON ACTH AND CORTISONE

Auditorium, Convention Hall

Presiding Officer

PHILIP S. HENCH, F.A.C.P., Rochester

A.M.

9:00 Present Status of ACTH and Adrenal Steroid Therapy in Medicine.

J. S. L. BROWNE, F.A.C.P., Professor of Medicine and Chairman of the Department, McGill University Faculty of Medicine; Physician and Director of McGill University Clinic, Royal Victoria Hospital; Montreal.

9:30 Adrenocorticotrophic Hormone and Adrenal Steroids in the Management of Infectious Diseases.

WESLEY W. SPINK, F.A.C.P., Professor of Medicine, University of Minnesota Medical School, Minneapolis.

10:00 The Role of ACTH, Cortisone and Hydrocortisone in Surgery.

WILLIAM E. ABBOTT, M.D., (by invitation), Associate Professor of Surgery, Western Reserve University School of Medicine, Cleveland.

10:30 Chronic Hypercortisonism.

HOWARD F. POLLEY, F.A.C.P., Assistant Professor of Medicine, University of Minnesota (Mayo Foundation); Consultant in Medicine, Mayo Clinic; Rochester.

11:00 ADJOURNMENT, followed by Panel Discussions and Clinical-Pathological Conferences (Consult Panel Program).

Friday, April 29, 1955

VI. SYMPOSIUM ON PREVENTIVE MEDICINE

Auditorium, Convention Hall

Presiding Officer

MAURICE C. PINCOFFS, M.A.C.P., Baltimore

A.M.

9:00 General Aspects of the Prevention of Rheumatic Fever.

JOHN P. HUBBARD, F.A.C.P., Professor of Public Health and Preventive Medicine, University of Pennsylvania School of Medicine, Philadelphia.

9:20 Prevention of Acute Nephritis.

CHARLES H. RAMMELKAMP, JR., F.A.C.P., Professor of Medicine and Associate Professor of Preventive Medicine, Western Reserve University School of Medicine, Cleveland.

9:40 **The Prevention of Respiratory Infections Within Families.**
JOHN H. DINGLE, M.D., (by invitation), Professor of Preventive Medicine and Associate Professor of Medicine, Western Reserve University School of Medicine, Cleveland.

10:00 **The Clinical Epidemiology of Poliomyelitis.**
DOROTHY M. HORSTMANN, F.A.C.P., Associate Professor of Preventive Medicine, Yale University School of Medicine, New Haven.

10:20 **The Current Status of the Control of Influenza.**
THOMAS FRANCIS, JR., M.D., (by invitation), Professor of Epidemiology, University of Michigan Medical School, Ann Arbor.

10:40 **The Seasonal Incidence of Patent Ductus Arteriosus and Maternal Rubella.**
DAVID D. RUTSTEIN, M.D., (by invitation), Professor of Preventive Medicine, Harvard Medical School, Boston.

11:00 ADJOURNMENT, followed by Panel Discussions and Clinical-Pathological Conferences (Consult Panel Program).

Friday, April 29, 1955

VII. SYMPOSIUM ON INFECTION

Ballroom, Third Floor, Convention Hall

Presiding Officer

WESLEY W. SPINK, F.A.C.P., Minneapolis

A.M.

9:00 **The Chemoprophylaxis of Infection.**
LOUIS WEINSTEIN, F.A.C.P., Associate Professor of Medicine, Boston University School of Medicine; Lecturer on Infectious Diseases, Harvard Medical School; Chief, Department of Infectious Diseases, Massachusetts Memorial Hospitals; Boston.

9:30 **Microbial Resistance to Antibiotics.**
MARK H. LEPPER, (Associate), Professor of Medicine, University of Illinois College of Medicine, Chicago.

9:55 **Management of Urinary Infections.**
EDWARD N. COOK, M.D., (by invitation), Associate Professor of Urology, University of Minnesota (Mayo Foundation); Consultant in Urology, Mayo Clinic; Rochester.

10:15 **The Re-evaluation of Sulfonamide Therapy.**
ELLARD M. YOW, (Associate), Associate Professor of Medicine, Baylor University College of Medicine, Houston.

10:40 **Allergic Reactions to Antibiotic and Sulfonamide Drugs.**
FRANCIS C. LOWELL, M.D., (by invitation), Associate Professor of Medicine, Boston University School of Medicine; Member, Robert Dawson Evans Memorial; Boston.

11:00 ADJOURNMENT, followed by Panel Discussions and Clinical-Pathological Conferences (Consult Panel Program).

PANEL DISCUSSIONS AND CLINICAL–PATHOLOGICAL CONFERENCES

For the Panels, topics of intimate interest and practical value to all members of the College have been chosen. Qualified men have been selected as Moderators and Panelists. All Panels are scheduled from Tuesday through Friday from 11:40 A.M. to 1:00 P.M. at Convention Hall.

For the Panels, applicants may submit in writing three weeks before the Session, through the Executive Secretary of the College, any questions concerning any phase of the subjects listed. Moderators and Panel personnel will answer those questions which they feel are applicable to the subject under discussion, and will answer as many questions as time permits. Furthermore, Moderators will discuss, as time permits, questions submitted from the floor.

An entirely new feature will be a Clinical-Physiological Conference on Wednesday, April 27, from 11:40 A.M. to 1:00 P.M., at which will be discussed cases from the standpoint of the contribution to diagnosis and management of newer studies of disturbed physiology.

Clinical-Pathological Conferences are scheduled on Tuesday, Wednesday, Thursday and Friday, running concurrently with the Panel Discussions. However, there will be an additional Clinical-Pathological Conference, with two cases, on Friday afternoon, April 29, from 3:30 P.M. to 5:00 P.M., in the Auditorium, following the Fifth General Session. The clinical protocols of the cases to be presented will appear in a separate booklet to be sent with the formal program, so that members may have the opportunity of making their own diagnoses before the formal conferences. The clinical protocols of these interesting cases will be discussed by the clinicians, who are expected to make the correct diagnoses, and, perhaps, criticize the treatment. The postmortem findings, their interpretation and their integration with the clinical aspects will then be presented by the pathologist in whose department the case was autopsied. Moderators and conference personnel will answer questions that may arise, as time permits.

Tickets will be required for certain Panels and Clinical-Pathological Conferences as indicated in the headings of the charts following this page. Where capacities are limited, admission by ticket must be enforced. Applications for tickets to Panels may be made in advance by MEMBERS on a regular application form which will accompany the program. Tickets will also be available at the Registration Bureau, Convention Hall. NON-MEMBERS may not register for Panels by mail, but should secure their tickets directly at the Registration Bureau at the meeting.

PANEL DISCUSSIONS and CLINICAL-PATHOLOGICAL CONFERENCES

	Auditorium Convention Hall (Admission by badge; no tickets)	Ballroom 3rd Floor Convention Hall (Admission by badge; no tickets)	Room 200 Auditorium Floor Convention Hall (Admission by ticket only)	Room 1 3rd Floor Convention Hall (Admission by ticket only)	Room 300 3rd Floor Convention Hall (Admission by ticket only)	Center Bldg., East Exhibition Floor Convention Hall (Admission by badge; no tickets)	Center Bldg., West Exhibition Floor Convention Hall (Admission by badge; no tickets)
Capacity	**4,000**	**1,050**	**200**	**100**	**250**	**800**	**800**
Tuesday April 26	**CP-1 Clinical-Pathological Conference**	**P-2 Arrhythmias**	**P-3 Emotional Aspects in Cardiac Disease**	**P-4 Coma**	**P-5 Chronic Pulmonary Disease**	**P-6 New Techniques in Diagnosis and Management of Thyroid Disease**	**P-7 Ballistocardiography**
11:40 A.M. to 1:00 P.M.	Case I Moderator **Maurice C. Pincoffs Baltimore *Herrman L. Blumgart Boston **Wm. S. Middleton Madison *Wesley W. Spink Minneapolis Pathologist Benjamin Castleman Boston Case II Moderator *David P. Barr New York *Alexander B. Gutman New York *Richard H. Lyons Syracuse *Theodore L. Squier Milwaukee Pathologist *Tobias Weinberg Baltimore	Moderator *Charles E. Kossmann New York *Samuel Bellet Philadelphia *George M. Jones Dallas *David Scherf New York Conger Williams Boston	Moderator *Eugene B. Ferris Atlanta *William N. Chambers Hanover George L. Engel Rochester, N. Y. *George C. Ham Chapel Hill Morton Reiser Washington	Moderator *M. A. Blankenhorn Cincinnati Winslow J. Borkowski Philadelphia *Ray F. Farquharson Toronto W. Paul Havens Philadelphia Henry F. Lee Philadelphia	Moderator *Alvan L. Barach New York *Robert Charr Philadelphia Vernon Knight Nashville *George R. Meneely Nashville *D. W. Richards New York	Moderator *Sidney C. Werner New York *F. Raymond Keating Rochester, Minn. Robert Robbins Philadelphia *Edward Rose Philadelphia W. P. VanderLaan, Jr. Boston	Moderator *Benj. M. Baker, Jr. Baltimore Frank W. Davis, Jr. Baltimore *William Dock New York *Louis N. Katz Chicago Isaac Starr Philadelphia

*F.A.C.P.
**M.A.C.P.

PANEL DISCUSSIONS and CLINICAL-PATHOLOGICAL CONFERENCES

	Auditorium Convention Hall (Admission by badge; no tickets)	Ballroom 3rd Floor Convention Hall (Admission by badge; no tickets)	Room 200 Auditorium Floor Convention Hall (Admission by ticket only)	Room 1 3rd Floor Convention Hall (Admission by ticket only)	Room 300 3rd Floor Convention Hall (Admission by ticket only)	Center Bldg., East Exhibition Floor Convention Hall (Admission by badge; no tickets)	Center Bldg., West Exhibition Floor Convention Hall (Admission by badge; no tickets)
Capacity	4,000	1,050	200	100	250	800	800
Wednesday April 27 11:40 A.M. to 1:00 P.M.	P-8 **Hypertension** Moderator *Garfield G. Duncan Philadelphia Edward D. Freis Washington *William Goldring New York *Robert S. Palmer Boston *Henry A. Schroeder St. Louis	CPh-9 **Clinical-Physiological Conference** Moderator *Julius H. Comroe, Jr. Philadelphia *Lewis Dexter Boston John B. Hickam Durham J. L. Lilienthal, Jr. Baltimore	P-10 **Drug Addiction, Alcohol and Suicide** Moderator *Richard A. Kern Philadelphia *Joseph C. Doane Philadelphia *Joseph F. Hughes Philadelphia *Harris Isbell Lexington Mr. John Park Lee Philadelphia	P-11 **Syncope and Vertigo** Moderator *George A. Wolf, Jr. Burlington Sherman F. Gilpin, Jr. Philadelphia *John S. LaDue New York Rufus C. Morrow, Jr. Burlington Paul M. Zoll Boston	P-12 **Infections of the Kidney** Moderator *Howard F. Root Boston *Alex. M. Burgess Providence Edward W. Campbell Philadelphia *Carl C. Fischer Philadelphia *Harrison F. Flippin Philadelphia	P-13 **Clinical Hematology** Moderator *Frank H. Bethell Ann Arbor C. Lockard Conley Baltimore Clement A. Finch Seattle *R. Wayne Rundles Durham *C. J. D. Zarafonetis Philadelphia	P-14 **Renal Disease** Moderator *Herbert Chasis New York J. K. Clark Philadelphia *Kenneth G. Kohlstaedt Indianapolis Arthur J. Merrill Atlanta *John P. Merrill Boston

*F.A.C.P.

PANEL DISCUSSIONS and CLINICAL-PATHOLOGICAL CONFERENCES

	Auditorium Convention Hall (Admission by badge; no tickets)	Ballroom 3rd Floor Convention Hall (Admission by badge; no tickets)	Room 200 Auditorium Floor Convention Hall (Admission by ticket only)	Room 1 3rd Floor Convention Hall (Admission by ticket only)	Room 300 3rd Floor Convention Hall (Admission by ticket only)	Center Bldg., East Exhibition Floor Convention Hall (Admission by badge; no tickets)	Center Bldg., West Exhibition Floor Convention Hall (Admission by badge; no tickets)
Capacity	4,000	1,050	200	100	250	800	800
Thursday April 28 **11:40 A.M. to 1:00 P.M.**	**CP-15** **Clinical-Pathological Conference** Case I Moderator *Howard P. Lewis Portland *J. Edward Berk Detroit *Claude E. Forkner Boston *Thomas A. Warthin Boston Pathologist *Ferdinand C. Helwig Kansas City, Mo. Case II Moderator Roger O. Egeberg Los Angeles *Theo. J. Abernethy Washington *Paul B. Beeson New Haven *Chester S. Keefer Boston Pathologist William E. Ehrich Philadelphia	**P-16** **Cardiac Surgery** Moderator *Lewis Dexter Boston *E. Cowles Andrus Baltimore Robert P. Glover Philadelphia *William Likoff Philadelphia *Louis A. Soloff Philadelphia	**P-17** **Tips from the Dermatologist to the Internist** Moderator *Marion B. Sulzberger New York *Herman Beerman Philadelphia *Arthur C. Curtis Ann Arbor *John R. Haserick Cleveland *Walter B. Shelley Philadelphia		**P-18** **Parkinsonism** Moderator Lewis J. Doshay New York *Bernard J. Alpers Philadelphia *Roland P. Mackay Chicago *A. M. Ornsteen Philadelphia J. Lawrence Pool New York	**P-19** **Diabetes** Moderator *Arthur R. Colwell, Sr. Chicago *Frank N. Allan Boston *Jos. T. Beardwood, Jr. Philadelphia *E. Perry McCullagh Cleveland L. O. Underdahl Rochester, Minn.	**P-20** **Ulcerative Colitis** Moderator *Henry J. Tumen Philadelphia L. K. Ferguson Philadelphia *Sydney G. Margolin New York *Walter L. Palmer Chicago *Stewart G. Wolf, Jr. Oklahoma City

*F.A.C.P.

PANEL DISCUSSIONS and CLINICAL-PATHOLOGICAL CONFERENCES

	Auditorium Convention Hall (Admission by badge; no tickets)	Ballroom 3rd Floor Convention Hall (Admission by badge; no tickets)	Room 200 Auditorium Floor Convention Hall (Admission by ticket only)	Room 1 3rd Floor Convention Hall (Admission by ticket only)	Room 300 3rd Floor Convention Hall (Admission by ticket only)	Center Bldg., East Exhibition Floor Convention Hall (Admission by badge; no tickets)	Center Bldg., West Exhibition Floor Convention Hall (Admission by badge; no tickets)
Capacity	4,000	1,050	200	100	250	800	800
Friday April 29 **11:40 A.M. to 1:00 P.M.**	**CP-21** **Clinical-Pathological Conference** Case I Moderator *R. H. Kampmeier Nashville *Alex. M. Burgess Providence J. K. Clark Philadelphia *Edward Rose Philadelphia Pathologist *William G. Bernhard Newark Case II Moderator *Garfield G. Duncan Philadelphia *William Likoff Philadelphia *John P. Merrill Boston K. E. Paschkis Philadelphia Pathologist Ernest E. Aegerter Philadelphia	**P-22** **The Stroke Problem** Moderator *Edgar V. Allen Rochester, Minn. Robert A. Groff Philadelphia *C. H. Millikan Rochester, Minn. *Howard A. Rusk New York *Irving S. Wright New York	**P-23** **What's New in Pediatrics** Moderator Milton Rapoport Philadelphia A. M. Bongiovanni Philadelphia Wallace W. McCrory Philadelphia Waldo E. Nelson Philadelphia Joseph Stokes, Jr. Philadelphia	**P-24** **Fever of Undetermined Origin** Moderator *Wesley W. Spink Minneapolis *Charles L. Brown Philadelphia *Chester S. Keefer Boston *Clayton G. Loosli Chicago	**P-25** **The Internist as a Marriage Counselor** Moderator *O. Spurgeon English Philadelphia Lovett Dewees Glen Mills *Ferdinand Fetter Philadelphia William A. Steiger Philadelphia	**P-26** **Recent Development in the Treatment of Cancer** Moderator *Stanley P. Reimann Philadelphia Harry R. Draper Philadelphia Ralph Jones, Jr. Philadelphia *William H. Lewis, Jr. New York Ivan H. Smith London, Ont.	**P-27** **Antimicrobial Treatment** Moderator *Monroe J. Romansky Washington Vernon Knight Nashville Mark H. Lepper Chicago T. F. McNair Scott Philadelphia *Louis Weinstein Brookline

*F.A.C.P.

PANEL DISCUSSIONS and CLINICAL-PATHOLOGICAL CONFERENCES

	Auditorium Convention Hall (Admission by badge; no tickets)	Ballroom 3rd Floor Convention Hall (Admission by badge; no tickets)	Room 200 Auditorium Floor Convention Hall (Admission by ticket only)	Room 1 3rd Floor Convention Hall (Admission by ticket only)	Room 300 3rd Floor Convention Hall (Admission by ticket only)	Center Bldg., East Exhibition Floor Convention Hall (Admission by badge; no tickets)	Center Bldg., West Exhibition Floor Convention Hall (Admission by badge; no tickets)
Capacity	4,000	1,050	200	100	250	800	800
Friday April 29 **3:30 P.M. to 5:00 P.M.**	**CP-28** **Clinical-Pathological Conference** Case I Moderator **O. H. Perry Pepper Philadelphia *Sol Katz Washington Clement A. Finch Seattle *John E. Deitrick Philadelphia Pathologist *W. A. D. Anderson Coral Gables Case II Moderator **O. H. Perry Pepper Philadelphia *Charles L. Brown Philadelphia *J. Russell Elkinton Philadelphia *H. M. Thomas, Jr. Baltimore Pathologist *Peter A. Herbut Philadelphia						

* F.A.C.P.
** M.A.C.P.

THE CLINIC SESSIONS

Color Television of Medical Clinics

The following series of clinics will be televised in color daily, Tuesday through Friday, between 9:00 A.M. to 11:00 A.M., from the Mills Building of the Philadelphia General Hospital to Convention Hall, Exhibition Floor.

Various institutions and their respective staffs are co-operating. Due to changing programs from one clinic to another, a slight lag will occur. However, it is believed that the times indicated will be approximately correct. This program is made possible through the co-operation of the Smith, Kline and French Laboratories, of Philadelphia. This year large screens will be used, instead of the multiple small screens as formerly.

Admission by regular badge; no special tickets required.

Tuesday, April 26, 1955

WOMAN'S MEDICAL COLLEGE OF PENNSYLVANIA PRESENTS:

A.M.

9:00– 9:15 **The Use of Cortisone in the Prevention of Hemolytic Anemia of the Newborn Due to Rh Incompatibility.**
ABRAHAM M. FRUMIN, (Associate), Associate in Medicine.

9:15– 9:30 **Cushing's Syndrome, Case Presentation.**
MARY B. DRATMAN, M.D., (by invitation), Associate in Endocrinology and Instructor in Medicine, ELEANOR M. SMITH, M.D., (by invitation), Clinical Instructor in Medicine and Endocrinology, and DONALD R. COOPER, M.D., (by invitation), Associate Professor of Surgery.

TEMPLE UNIVERSITY SCHOOL OF MEDICINE PRESENTS:

9:30–11:00 **Normal and Abnormal Reflexes: How to Elicit Them and Their Significance.**
SHERMAN F. GILPIN, JR., M.D., (by invitation), Clinical Professor of Neurology.

Malignant Exophthalmos in Thyroid Disease.
WILLIAM H. PERLOFF, (Associate), Assistant Professor of Medicine.

Dermatologic Problems in Internal Medicine.
CARROLL S. WRIGHT, M.D., (by invitation), Professor and Head of the Department of Dermatology and Syphilology; JOHN B. ROXBY, JR., M.D., (by invitation), Instructor in Dermatology.

Treatment of Pemphigus: Combined KPAB and Cortisone.
CHRIS J. D. ZARAFONETIS, F.A.C.P., Associate Professor of Medicine.

Infantile Myoclonic Seizures.
HENRY W. BAIRD, III, M.D., (by invitation), Pediatric Neurologist, St. Christopher's Hospital.

Wednesday, April 27, 1955

WOMAN'S MEDICAL COLLEGE OF PENNSYLVANIA PRESENTS:

A.M.

9:00– 9:30 **Chest Conference.**

KATHARINE R. BOUCOT, F.A.C.P., **Moderator,** Professor of Preventive Medicine and Clinical Professor of Medicine.

THOMAS J. E. O'NEILL, M.D., (by invitation), Clinical Assistant Professor of Surgery.

JOHN J. REINHARD, M.D., (by invitation), Clinical Assistant Professor of Surgery.

MAURICE SONES, F.A.C.P., Assistant Professor of Medicine.

JACOB H. VASTINE, M.D., (by invitation), Professor of Radiology.

HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA PRESENTS:

9:30–11:00 **Angina and Plasma Lipids.**

PETER T. KUO, M.D., (by invitation), Associate in Medicine, and CLAUDE R. JOYNER, M.D., (by invitation), Instructor in Medicine.

Experimental Obesity in Animals.

JOHN R. BROBECK, M.D., (by invitation), Professor of Physiology.

The Artificial Kidney.

J. RUSSELL ELKINTON, F.A.C.P., Associate Professor of Medicine, and LEWIS W. BLUEMLE, JR., (Associate), Associate in Medicine.

New Antimalarial Drugs.

RALPH JONES, JR., (Associate), Associate Professor of Medicine.

Joint Aspiration and Hydrocortisone Injection.

JOSEPH L. HOLLANDER, F.A.C.P., Associate Professor of Clinical Medicine, and ROBERT MOORE, M.D., (by invitation), Visiting Associate in Medicine.

Intubation in Diagnosis and Management of Gastro-intestinal Disorders.

THOMAS E. MACHELLA, F.A.C.P., Associate Professor of Medicine, and WINSTON K. SHOREY, M.D., (by invitation), Associate in Medicine.

The Basis of Electrocardiographic Patterns.

ERNEST FRANK, M.S., (by invitation), Associate Professor of Electrical Engineering in Medicine, CALVIN F. KAY, F.A.C.P., Associate Professor of Medicine, and GEORGE E. SEIDEN, M.D., (by invitation), Associate in Medicine.

Thursday, April 28, 1955

EINSTEIN MEDICAL CENTER (NORTHERN DIVISION) PRESENTS:

A.M.

9:00– 9:15 **Post-cholecystectomy Syndrome.**

HENRY J. TUMEN, F.A.C.P., Professor of Clinical Gastro-enterology, University of Pennsylvania Graduate School of Medicine, and Gastro-enterologist.

9:15– 9:30 **Recent Developments in Histochemistry in Diagnosis and Experimental Medicine.**
HENRY BRODY, M.D., (by invitation), Assistant Professor of Pathology, Temple University School of Medicine, and Chief of Laboratory.

JEFFERSON MEDICAL COLLEGE PRESENTS:

9:30– 9:45 **Coarctation of the Aorta; Demonstration of Anatomic and Physiologic Defects.**
JOHN E. DEITRICK, F.A.C.P., Professor and Head of Department of Medicine, and J. E. CLARK, M.D., (by invitation), Resident in Medicine.

9:45–10:00 **Criteria for Operability of Patients with Chronic Hepatic Disease.**
W. PAUL HAVENS, M.D., (by invitation), Associate Professor of Microbiology.

10:10–10:25 **Early Recognition and Possible Prevention of Brain Lesions in Children.**
CHARLES F. MCKHANN, F.A.C.P., Professor and Head of Department of Pediatrics.

10:25–10:45 **Endocrine Clinic: Diagnostic and Therapeutic Problems in Sexually Abnormal Children; Cushing's Syndrome.**
K. E. PASCHKIS, M.D., (by invitation), Associate Professor of Medicine, J. J. RUPP, (Associate), Instructor in Medicine, S. M. WOLFE, M.D., (by invitation), Assistant in Medicine, and A. M. DIGEORGE, M.D., (by invitation), Fellow in Endocrinology.

10:45–11:00 **Diagnosis and Management of Hemophilic Arthropathies.**
LEANDRO M. TOCANTINS, F.A.C.P., Professor of Clinical and Experimental Medicine, A. F. DEPALMA, M.D., (by invitation), Professor of Orthopedic Surgery, and R. CARROL, M.D., (by invitation), Fellow in Hematology.

Friday, April 29, 1955

A.M.

9:00– 9:15 **Newer Criteria in the Management of Metastatic Lesion of Breast Cancer.**
ARTHUR STEINBERG, M.D., (by invitation), Associate in Clinical Pathology and Chief of Endocrine Laboratory, Einstein Medical Center, Southern Division.

9:15– 9:30 **Hypersplenism as a Manifestation of Subacute Bacterial Endocarditis and of Toxic States.**
IRVING WOLDOW, M.D., (by invitation), Head of Hematology Department, Einstein Medical Center, Northern Division, and Instructor in Medicine, Jefferson Medical College.

UNIVERSITY OF PENNSYLVANIA GRADUATE SCHOOL OF MEDICINE PRESENTS:

9:30–10:00 **Demonstration of Instruments and Techniques Useful in Teaching, Diagnosis and Research in Cardiovascular Disease.**
SAMUEL BELLET, F.A.C.P., Professor of Clinical Cardiology, DAVID GELFAND, F.A.C.P., Associate in Cardiology, and GEORGE R. MOFFITT, M.D., (by invitation), Associate in Medicine.

PRESBYTERIAN HOSPITAL PRESENTS:

10:00–11:00 **Experimental Study of Surgical Methods of Treatment of Valvular Insufficiencies.**

Introduction: ROBERT P. GLOVER, M.D., (by invitation), Chief of Department of Thoracic and Cardiac Surgery and Director of the Cardiovascular Research Laboratories.

Mitral Insufficiency: J. C. DAVILA, M.D., (by invitation), Assistant Director, Cardiovascular Research Laboratories.

Aortic Insufficiency: ROBERT G. TROUT, M.D., (by invitation), Chief Resident, Department of Thoracic and Cardiac Surgery.

Clinical Significance: O. HENRY JANTON, (Associate), Associate in Cardiology and Director of the Clinical Cardiovascular Laboratory.

THE CLINIC SESSIONS

Clinics at Hospitals

The regular Hospital Clinics will be conducted on Tuesday and Thursday from 9:00 A.M. to 11:00 A.M. **Admission to the Hospital Clinics will require special tickets,** which will be issued to MEMBERS in advance of the Session and to NON-MEMBERS directly at the Registration Bureau at Convention Hall. Application forms for tickets for the Hospital Clinics, Panel Discussions and Clinical-Pathological Conferences will be sent to all members with the program.

The Committee on Clinics is committed to a program of clinics in the true sense of that term—patients will be shown and discussed. A wide range of medical topics important to the clinician is offered.

Many of the clinics will be held in Convention Hall; only clinics at hospitals convenient to the hotel headquarters and/or Convention Hall will be held in the hospitals themselves. Therefore, each individual should note carefully the site of the clinic he wishes to attend. Special busses will operate from the Benjamin Franklin and Bellevue-Stratford Hotels to Convention Hall, and these busses may suitably be used for the clinics not only at Convention Hall, but near-by, such as the Hospital of the University of Pennsylvania, Philadelphia General Hospital and the Veterans Administration Hospital.

Members are requested not to attempt to split clinics with one another. Tickets will be required for each and every Hospital Clinic, unless specifically otherwise mentioned. The co-operation of every one in securing his clinic tickets will assist greatly in distributing the audience according to the capacity of each meeting room. It is self-evident that a clinic arranged for fifty will lose its value for all if a hundred crowd in. Ticket registration, naturally, is the only effective method of keeping the attendance within the capacities indicated.

Member registration blanks for the clinics should be filled out and returned to the Executive Secretary promptly. Upon receipt at the College Office, proper tickets will be selected and held at the Registration Bureau in Convention Hall, or, on the request of the member, will be mailed to him. Reservations by mail cannot be accepted after April 4, but reservations may be made in person at the Registration Bureau on the afternoon preceding any clinic day, providing tickets are still available.

Members who reserve clinic tickets are urged to notify the Executive Secretary, and to return their tickets, if they find they will be unable to attend.

PROGRAM OF HOSPITAL CLINICS

Tuesday, April 26, 1955

A CHILDREN'S HOSPITAL

(18th and Bainbridge Streets)

Nurses' Home, Auditorium

(Capacity,125)

(Ten minutes walking distance from central city.
Bainbridge St. is 600 South)

JOSEPH STOKES, JR., Presiding

9:00– 9:25 Clinical Evaluation of Cerebral Hemi-decortication in the Pediatric Age Group.
EUGENE B. SPITZ.

9:25– 9:50 Early Recognition of Leukemia.
IRVING J. WOLMAN.

9:50–10:05 INTERMISSION—Coffee and doughnuts.

10:05–10:35 Recent Advances in Virus Diseases.
T. F. MCNAIR SCOTT.

10:35–11:00 Certain Aspects of Renal Diseases.
MILTON RAPOPORT.

B ALBERT EINSTEIN MEDICAL CENTER

Room 200, Auditorium Floor, Convention Hall

(Capacity, 200)

DAVID R. MERANZE, Presiding

9:00– 9:15 Vanishing Tumor of the Lung. A Manifestation of Congestive Heart Failure.
THEODORE H. MENDELL and SOLOMON S. MINTZ.

9:15– 9:30 Pulmonary Arteriovenous Aneurysms in Father and Son, Associated with Congenital Familial Telangiectasis.
SAMUEL BAER.

9:30– 9:45 Management of Arterial Occlusions of the Extremities.
MYER NAIDE.

9:45–10:00 Visualization of the Aorta.
HAROLD J. ISARD.

Hospital Clinics—Tuesday, April 26, 1955

10:00–10:15 INTERMISSION.

THEODORE H. MENDELL, Presiding.

10:15–10:30 Cardiac Sarcoidosis.
BENJAMIN A. GOULEY.

10:30–10:45 Myxedema Heart.
FRED R. SHECHTER and ARTHUR STEINBERG.

10:45–11:00 Cardiac Involvement in Trichinosis.
WILLIAM I. HEINE.

C GERMANTOWN DISPENSARY AND HOSPITAL

Room 1, 3rd Floor, Convention Hall

(Capacity, 100)

JOHN E. DEITRICK, Presiding

9:00– 9:25 Treatment of Paroxysmal Tachycardia in Pregnancy.
RALPH W. MAYS.

9:25– 9:50 Management of Chronic Renal Failure.
WALLACE G. MCCUNE.

9:50–10:00 INTERMISSION.

10:00–10:25 The Significance of Jaundice in Medical Diagnosis.
C. JOSEPH MILLER.

10:25–11:00 Medical Management of Commissurotomy Candidates.
W. LAWRENCE CAHALL.

D GRADUATE HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

(19th and Lombard Streets)

North Lecture Room

(Capacity, 125)

JACOB J. KOHLHAS, Presiding

9:00– 9:55 Inflammatory Diseases of the Intestinal Tract.
HENRY L. BOCKUS, THOMAS A. JOHNSON, VALDES DAPENA, JAMES L. A. ROTH, HERBERT R. HAWTHORNE and ARTHUR FINKELSTEIN.

9:55–10:05 INTERMISSION.

10:05–11:00 Newer Treatment of Diabetic Retinitis with Demonstrations.
JOSEPH T. BEARDWOOD, JR., ROBERT H. TRUEMAN and JULIUS J. SMITH.

Hospital Clinics—Tuesday, April 26, 1955

E-1 HAHNEMANN MEDICAL COLLEGE AND HOSPITAL

(Broad Street above Race)

Elkins Amphitheater, 3rd Floor

(Capacity, 175)

(Within ten minutes walking distance of central city. Walk north on Broad St. to hospital between Race and Vine Sts.)

CHARLES M. THOMPSON, Presiding

9:00– 9:30 The Diagnosis of Hepato-biliary Disease and Patency of Bile Passages by the "Decholin" Test.
JOSEPH M. GAMBESCIA and WILLIAM C. SHOEMAKER.

9:30– 9:50 The Demonstration of Common Duct Obstruction with the Use of Biligrafin.
FRED S. WINTER.

9:50–10:15 The Management of Hepatic Parenchymal Insufficiency and the Effect of Co-enzyme Factor.
CHARLES M. THOMPSON and PHILLIP LISAN.

10:15–10:20 INTERMISSION.

10:20–10:40 Presentation of Cases with Collagen Disturbances.
CARROLL F. BURGOON, JR.

10:40–11:00 The Permanent Management of Collagen Disorders with Zinc Corticotropin.
HARRY E. BANGHART.

E-2 HAHNEMANN MEDICAL COLLEGE AND HOSPITAL

(Broad Street above Race)

Klahr Auditorium

(Capacity, 500)

(Within ten minutes walking distance of central city. Walk north on Broad St. to hospital between Race and Vine Sts.)

GEORGE D. GECKELER, Presiding

9:00– 9:30 Demonstration of Clinical Problems Amenable to Cardiac Surgery.
WILLIAM LIKOFF.

9:30– 9:50 Subjective Pain Relief in Angina Pectoris from the Use of Stellate Ganglion Block.
ALFRED J. CATENACCI.

9:50–10:05 INTERMISSION.

10:05–10:35 Staphylococcic Subacute Bacterial Endocarditis.
DANIEL J. MARINO, AMEDEO BONDI and RICHARD K. WATANABE.

10:35–11:00 The Management of Acute Embolic Occlusion of the Aorta, Iliac, and Femoral Arteries.
FRANK TROPEA, JR., and ALEXANDER W. ULIN.

Hospital Clinics—Tuesday, April 26, 1955

F-1 HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

(36th and Spruce Streets)

Alumni Hall

(Capacity, 300)

CARL K. FRIEDLAND, Presiding

9:00– 9:55 The Relationship of Gastro-intestinal Lesions to Pain in Coronary Artery Distribution.
WINSTON K. SHOREY, CHARLES C. WOLFERTH and I. S. RAVDIN.

9:55–10:05 INTERMISSION.

10:05–10:55 Congestive Heart Failure. Clinical-Physiological Panel.
ISAAC STARR, HARRY F. ZINSSER, JR., and RUSSELL D. SQUIRES.

F-2 HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

(36th and Spruce Streets)

Surgical Amphitheater

(Capacity, 150)

ADOLPH J. CRESKOFF, Presiding

9:05– 9:55 Management of Patients with Incurable Cancer.
RALPH JONES, JR., GEORGE M. AUSTIN, WILLIAM T. FITTS, JR., RICHARD H. CHAMBERLAIN and SYLVAN H. EISMAN.

9:55–10:05 INTERMISSION.

10:05–10:55 Clinical-Hematological Panel.
Malignant Dyscrasias.
JOHN W. FROST.
Hemoglobin.
TIMOTHY R. TALBOT, JR.
Blood Coagulation.
HAROLD A. WURZEL.

G JEFFERSON HOSPITAL

(10th and Sansom Streets)

Clinical Amphitheater, 1st Floor

(Capacity, 300)

(Enter hospital between 10th and 11th Sts.)

C. WILMER WIRTS, Presiding

9:00– 9:15 Introduction.
C. WILMER WIRTS.

9:15–10:00 Peptic Ulcer, Hiatus Hernia, and Gastritis:
a) Presentation of Cases.
PAUL J. CIMOCH, ARTHUR J. WEISS and TIBOR BODI.

Hospital Clinics—Tuesday, April 26, 1955

b) Mechanism of Bleeding and the Use of Whole Blood Transfusion.
LEANDRO M. TOCANTINS.
c) Surgical Treatment.
JOHN Y. TEMPLETON, 3RD.

10:00–10:15 INTERMISSION.

10:15–11:00 Esophageal Varices:
a) Presentation of Cases.
ARTHUR J. WEISS and TIBOR BODI.
b) Diagnosis by Esophagoscopy.
F. JOHNSON PUTNEY.
c) Diagnosis by Roentgen-ray.
GERALD D. DODD.
d) Balloon Tamponade and Medical Treatment.
PAUL J. CIMOCH.
e) Surgical Management.
KENNETH E. FRY.

H

LANKENAU HOSPITAL

(Lancaster Ave., West of City Line, Overbrook)

Auditorium

(Capacity, 350)

MALCOLM W. MILLER, Presiding

Modern Therapy of Cancer

9:00– 9:40 Attempts at Chemotherapy of Cancer.
STANLEY P. REIMANN.

9:40–10:20 The Cobalt 60 Theratron in the Treatment of Cancer.
THOMAS C. POMEROY.

10:20–10:30 INTERMISSION.

10:30–11:00 Inspection of Cobalt 60 Theratron Unit in Lankenau Hospital.

Transportation will be provided by Bus
(Courtesy of Women's Board of the Lankenau Hospital)
Leave: Benjamin Franklin Hotel at 8:20 A.M.
Leave: Bellevue-Stratford Hotel at 8:30 A.M.
Return: Following the Inspection of Cobalt 60 Theratron Unit, directly to Convention Hall.

J

PENNSYLVANIA HOSPITAL

(8th and Spruce Streets)

Chapel

(Capacity, 150)

PERRY S. MACNEAL, Presiding

9:00– 9:25 The Diagnosis and Treatment of Chronic Hepatic Disease.
W. PAUL HAVENS.

9:25– 9:50 Endocrine Problems in Childhood.
ALFRED M. BONGIOVANNI.

Hospital Clinics—Tuesday, April 26, 1955

9:50–10:10 INTERMISSION.

10:10–10:35 The Changing Nature of Pulmonary Infection.
ROBERT CHARR.

10:35–11:00 Problems in the Diagnosis and Treatment of Diseases of the Gastrointestinal Tract.
ALEXANDER RUSH.

K **PHILADELPHIA GENERAL HOSPITAL**

(34th Street below Spruce)

Nurses Auditorium

(Capacity, 200)

HARRISON F. FLIPPIN, Presiding

9:00– 9:30 Recent Advances in the Use of Antibiotics.
HARRISON F. FLIPPIN.

9:30– 9:35 Questions and Answers.

9:35–10:05 Nutrition in Congestive Heart Failure.
MICHAEL G. WOHL.

10:05–10:10 Questions and Answers.

10:10–10:25 INTERMISSION.

10:25–10:55 Recent Advances in Therapy of Cardiac Arrhythmias.
SAMUEL BELLET.

10:55–11:00 Questions and Answers.

L **PRESBYTERIAN HOSPITAL**

Room 19, 3rd Floor, Convention Hall

(Capacity, 100)

FERDINAND FETTER, Presiding

9:00– 9:55 Group Therapy Session on Alcoholism.
C. NELSON DAVIS, R. PHILIP CUSTER and HENRY TESCH.

9:55–10:05 INTERMISSION.

10:05–11:00 Late Results of Cardiac Surgery.
ROBERT P. GLOVER, O. HENRY JANTON and THOMAS J. E. O'NEILL.

M **TEMPLE UNIVERSITY HOSPITAL**

Room 300, 3rd Floor, Convention Hall

(Capacity, 250)

WILLIAM A. STEIGER, Presiding

9:00– 9:50 Problems in Psychosomatic Medicine.
O. SPURGEON ENGLISH and EDWARD WEISS.

9:50–10:00 INTERMISSION.

Hospital Clinics—Tuesday, April 26, 1955

10:00–10:30 Differential Diagnosis of Dysphagia and the Medical and Surgical Treatment of its Causes.
STANLEY H. LORBER and CHARLES M. NORRIS.

10:30–11:00 Problems in the Differential Diagnosis of Jaundice.
HARRY SHAY.

N UNITED STATES NAVAL HOSPITAL

(17th Street and Pattison Avenue)

(See Thursday only)

O VETERANS ADMINISTRATION HOSPITAL

(University and Woodland Avenues)

Auditorium

(Capacity, 250)

(From central city take Trolley Car No. 13 or 42 west on Walnut St. to 39th and Spruce Sts. Hospital is one block south on 39th St. Hospital is 5 minutes walking distance from Convention Hall.)

HENRY P. CLOSE, Presiding

9:00– 9:15 Cryoglobulinemia.
RALPH M. MYERSON.

9:15– 9:40 Therapy of Pulmonary Emphysema Including Use of I^{131}.
HENRY P. CLOSE.

9:40–10:00 Use of Pneumography in the Diagnosis of Retroperitoneal Neoplasms.
GEORGE T. WOHL.

10:00–10:15 INTERMISSION—Coffee.

10:15–11:00 Lesions of the Small Bowel.
JOHN H. WILLARD.

P WOMAN'S MEDICAL COLLEGE OF PENNSYLVANIA

Clinics to be held at Philadelphia General Hospital

(34th Street below Spruce)

Mills Auditorium

(Capacity, 250)

WILLIAM G. LEAMAN, Presiding

9:00– 9:40 The Complications of Myocardial Infarction, and Their Management.
GEORGE C. GRIFFITH, Los Angeles.

9:40–10:05 The Use of Digitalis in Coronary Heart Disease.
ARTHUR C. DEGRAFF, New York.

10:05–10:20 INTERMISSION.

10:20–11:00 Modern Management of Severe Hypertension.
HENRY A. SCHROEDER, St. Louis.

Hospital Clinics—Thursday, April 28, 1955

Thursday, April 28, 1955

A CHILDREN'S HOSPITAL

(18th and Bainbridge Streets)

Nurses Home Auditorium

(Capacity, 125)

(Ten minutes walking distance from central city. Bainbridge St. is 600 South.)

JOHN PORTER SCOTT, Presiding

9:00– 9:25 Problems of Current Interest in Pediatric Surgery.
C. EVERETT KOOP.

9:25– 9:50 Techniques of Pediatric Radiology.
JOHN W. HOPE.

9:50–10:05 INTERMISSION—Coffee and doughnuts.

10:05–10:35 Problems of Current Interest in Pediatric Endocrinology.
ALFRED M. BONGIOVANNI.

10:35–11:00 What Comes Next in Management of Prematurity.
HENRY F. LEE.

B ALBERT EINSTEIN MEDICAL CENTER

Room 300, 3rd Floor, Convention Hall

(Capacity, 250)

SAMUEL BAER, Presiding

9:00– 9:15 Guillain-Barre Syndrome.
RAPHAEL H. GREENSTEIN.

9:15– 9:30 Alimentary Lipemia in Atherosclerosis.
LEON SCHWARTZ.

9:30– 9:45 Vectorcardiographic and Electrocardiographic Correlation with Autopsy Findings.
ALVIN M. SOFFE.

9:45–10:00 The Post-Cholecystectomy Syndrome.
HENRY J. TUMEN.

10:00–10:15 INTERMISSION.

HAROLD J. ISARD, Presiding

10:15–10:30 Hemophilioid States.
IRVING WOLDOW.

10:30–10:45 Metabolic Bone Disease with Special Emphasis on Post-Menopausal Osteoporosis.
MICHAEL G. WOHL.

10:45–11:00 Cyclic Nature of Thyrotoxicosis. Problems in Diagnosis.
NORMAN G. SCHNEEBERG.

Hospital Clinics—Thursday, April 28, 1955

C GERMANTOWN DISPENSARY AND HOSPITAL

Room 101, Exhibition Floor, Convention Hall

(Capacity, 100)

GULDEN MACKMULL, Presiding

9:00– 9:25 Medical Management of Inoperable Bronchiectasis.
DAVID E. REIBER.

9:25– 9:50 A Regimen for the Treatment of Osteoporosis with Methyl Androstenediol.
HARRY E. BANGHART.

9:50–10:00 INTERMISSION.

10:00–10:35 Treatment of Peripheral Circulatory Insufficiency: Arterial, Venous.
EDWARD B. POLIN and ROBERT P. WATERHOUSE.

10:35–11:00 Individualized Treatment of Chronic Hypertension.
THOMAS W. CLARK.

D GRADUATE HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

(19th and Lombard Streets)

North Lecture Room

(Capacity, 125)

EDWARD STEINFIELD, Presiding

9:00– 9:55 Evaluation of Hemolytic Phenomena.
MAX M. STRUMIA, Bryn Mawr, and LAWRENCE H. BEIZER.

9:55–10:05 INTERMISSION.

10:05–11:00 Hepatic and Renal Manifestations of Sarcoidosis.
HAROLD L. ISRAEL, MAURICE SONES and GERALD KLATSKIN, New Haven.

E-1 HAHNEMANN MEDICAL COLLEGE AND HOSPITAL

(Broad Street above Race)

Elkins Amphitheater, 3rd Floor

(Capacity, 175)

(Within ten minutes walking distance of central city. Walk north on Broad St. to hospital between Race and Vine Sts.)

LOWELL L. LANE, Presiding

9:00– 9:25 Short-term Therapy of Streptococcus Viridans Endocarditis.
FRANKLIN C. MASSEY and LOWELL L. LANE.

9:25– 9:50 Systemic and Gastro-intestinal Side Effects of Ureteroenterostomy.
EDWARD W. CAMPBELL and G. JOHN GISLASON.

9:50–10:05 INTERMISSION.

Hospital Clinics—Thursday, April 28, 1955

10:05–10:35 Per-oral Endoscopy in Patients with Cardiovascular Disease.
WALTER H. MALONEY.

10:35–11:00 Early X-Ray Examination and Early Operative Management in Selected Cases of Gastro-intestinal Hemorrhage.
RICHARD M. SPROCH and PAUL J. GROTZINGER.

E-2 HAHNEMANN MEDICAL COLLEGE AND HOSPITAL

(Broad Street above Race)

Klahr Auditorium

(Capacity, 500)

(Within ten minutes walking distance of central city. Walk north on Broad St. to hospital between Race and Vine Sts.)

CHARLES L. BROWN, Presiding

9:00– 9:50 Clinical Syndromes Associated with Lymphoma.
CHARLES L. BROWN and JOSEPH E. IMBRIGLIA.

9:50–10:05 INTERMISSION.

10:05–10:30 The Use of Dionsil in Bronchography.
J. ANTRIM CRELLIN, SR., and J. STAUFFER LEHMAN.

10:30–11:00 Teaching Cardiac Auscultation by Endless Loop Tape Recordings.
GEORGE D. GECKELER and DANIEL MASON.

F-1 HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

(36th and Spruce Streets)

Alumni Hall

(Capacity, 300)

O. H. PERRY PEPPER, Presiding

Man Made Diseases

9:05– 9:20 Transfusion Reaction. Recovery without Dialysis.
EARL S. BARKER.

9:20– 9:35 Transfusion Reaction. Recovery with Dialysis.
LEWIS W. BLUEMLE, JR.

9:35– 9:55 Digitalis Intoxication.
CALVIN F. KAY.

9:55–10:05 INTERMISSION.

10:05–10:20 Fungus Disease.
EDWARD D. DELAMATER.

10:20–10:35 Bacterial Disease.
HARRISON F. FLIPPIN.

10:35–10:55 Hyperadrenocorticism.
ERNEST M. BROWN, JR.

Hospital Clinics—Thursday, April 28, 1955

F-2 HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

(36th and Spruce Streets)

Surgical Amphitheater

(Capacity, 150)

T. GRIER MILLER, Presiding

9:05– 9:20 The Relative Benignancy of Chronic Glomerulonephritis.
J. K. CLARK.

9:20– 9:35 Angina Following Ingestion of Fat.
CLAUDE R. JOYNER and PETER T. KUO.

9:35– 9:50 The Significance of a Subnormal Metabolic Rate.
EDWARD ROSE.

9:50–10:05 INTERMISSION.

10:05–10:20 Ischemic Cardiac Pain Relieved by Nor-Epinephrine.
JOHN J. SAYEN.

10:20–10:35 Interstitial Pulmonary Fibrosis Treated with ACTH.
SIMON S. LEOPOLD.

10:35–10:50 Therapeutics and Their Psychotherapeutic Effects upon the Physician.
CARL K. FRIEDLAND.

G JEFFERSON HOSPITAL

(10th and Sansom Streets)

Clinical Amphitheater, 1st Floor

(Capacity, 300)
(Enter hospital between 10th and 11th Sts.)

C. WILMER WIRTS, Presiding

9:00– 9:05 Introduction.
C. WILMER WIRTS.

9:05–10:00 Small Intestine: Tumors, Hereditary Hemorrhagic Telangiectasis, Meckel's Diverticulum:

a) Presentation of Cases.
PAUL J. CIMOCH, ARTHUR J. WEISS and TIBOR BODI.

b) Roentgen Diagnosis.
GERALD D. DODD.

c) Medical Management.
LEANDRO M. TOCANTINS.

d) Pathology.
ROBERT L. BRECKENRIDGE.

e) Surgical Management.
FREDERICK B. WAGNER, JR.

10:00–10:15 INTERMISSION.

Hospital Clinics—Thursday, April 28, 1955

10:15–11:00 Lesions of the Colon:

a) Presentation of Cases.
PAUL J. CIMOCH, ARTHUR J. WEISS and TIBOR BODI.

b) Roentgen Diagnosis.
GERALD D. DODD.

c) Medical Management.
C. WILMER WIRTS.

d) Surgical Management.
W. BOSLEY MANGES.

H

LANKENAU HOSPITAL

Room 1, 3rd Floor, Convention Hall

(Capacity, 100)

RENDALL R. STRAWBRIDGE, Presiding

Management of Hyperthyroidism

9:00–10:00 Medical.
J. J. RUPP.

10:00–10:15 INTERMISSION.

10:15–11:00 Surgical.
LAWRENCE SINGMASTER.

J

PENNSYLVANIA HOSPITAL

(8th and Spruce Streets)

Chapel

(Capacity, 150)

PERRY S. MACNEAL, Presiding

9:00– 9:25 The Cervical Root Syndrome.
RICHARD T. SMITH.

9:25– 9:50 Case Presentations of Uncommon Metabolic Diseases.
PERRY S. MACNEAL.

9:50–10:10 INTERMISSION.

10:10–10:35 Experiences with Radioactive Iodine in the Treatment of Cardiovascular Disease.
JOSEPH A. WAGNER.

10:35–11:00 Two Cases of Subacute Bacterial Endocarditis Requiring Unusual Therapy.
MARTIN H. WENDKOS.

Hospital Clinics—Thursday, April 28, 1955

K-1 PHILADELPHIA GENERAL HOSPITAL

(34th Street below Spruce)

Nurses Auditorium

(Capacity, 200)

DAVID N. KREMER, Presiding

9:00– 9:30 Unusual Aspects of Sarcoidosis.
EDWARD S. MCCABE.

9:30– 9:35 Questions and Answers.

9:35–10:05 Splenoportography. (Visualization of the Splenic and Portal Veins by Means of Injecting Contrast Media Directly into the Spleen.)
DONALD R. COOPER.

10:05–10:10 Questions and Answers.

10:10–10:25 INTERMISSION.

10:25–10:55 Chronic Lead Poisoning with Myxedema Treated with Versonate.
HOWARD U. KREMER.

10:55–11:00 Questions and Answers.

K-2 PHILADELPHIA GENERAL HOSPITAL

(34th Street below Spruce)

Mills Auditorium

(Capacity, 250)

SAMUEL BELLET, Presiding

Symposium on Diagnostic Methods in Cardiovascular Disease

(The Functioning of a Hospital Diagnostic Clinic)

9:00– 9:15 Electrocardiography.
SAMUEL BELLET.

9:15– 9:30 Vectorcardiography.
JOHN R. URBACH.

9:30– 9:50 Phonocardiography.
DAVID GELFAND.

9:50–10:00 INTERMISSION.

10:00–10:15 Ballistocardiography.
A. J. HEISEN.

10:15–10:30 Cardiac Fluoroscopy.
DAVID FINKELSTEIN.

10:30–10:45 Cardiac Catheterization.
RICHARD S. MONHEIT and GEORGE R. MOFFITT.

10:45–11:00 Cardiac Work Classification Unit.
DAVID GELFAND.

Hospital Clinics—Thursday, April 28, 1955

L

PRESBYTERIAN HOSPITAL

Room 200, Auditorium Floor, Convention Hall

(Capacity, 200)

TRUMAN G. SCHNABEL, Presiding

9:00– 9:55 Hematology Clinic.
R. PHILIP CUSTER and JAMES BUTCHER.

9:55–10:05 INTERMISSION.

10:05–11:00 Endocrinologic Problems and Their Management.
MARTIN C. SAMPSON.

M

TEMPLE UNIVERSITY HOSPITAL

Room 19, 3rd Floor, Convention Hall

(Capacity, 100)

JACOB ZATUCHNI, Presiding

9:00– 9:50 Treatment of Scleroderma and Conditions of Increased Fibrosis with p-Aminobenzoate.
CHRIS J. D. ZARAFONETIS.

9:50–10:00 INTERMISSION.

10:00–10:30 Medical and Neurosurgical Treatment of Parkinson's Disease.
SHERMAN F. GILPIN, JR., and HENRY T. WYCIS.

10:30–11:00 Hirsutism: A Manifestation of Juvenile Hypothyroidism.
WILLIAM H. PERLOFF.

N

UNITED STATES NAVAL HOSPITAL

(17th Street and Pattison Avenue)

Lecture Room

(Capacity, 100)

LESTER J. POPE, Presiding

9:00– 9:25 Sphincterotomy in Chronic Relapsing Pancreatitis.
HENRY L. BOCKUS.

9:25– 9:50 Primary Pulmonary Hypertension:
Physiology—ROBERT E. FORSTER, II.
Clinical—JOSEPH B. VANDER VEER.

9:50–10:05 INTERMISSION.

10:05–10:35 Diagnosis and Treatment of Addison's Disease Associated with Hyperglycemia.
GARFIELD G. DUNCAN.

Hospital Clinics—Thursday, April 28, 1955

10:35–11:00 Diffuse Eosinophilic Granulomata from Ascariasis.
RICHARD A. KERN.

Transportation will be furnished by Navy bus
(Courtesy of Captain C. G. Clegg, MC, USN,
Commanding Officer, U. S. Naval Hospital)

Leave: Benjamin Franklin Hotel at 8:20 A.M.
Leave: Bellevue-Stratford Hotel at 8:30 A.M.
Return after clinics to Convention Hall.

O VETERANS ADMINISTRATION HOSPITAL

(University and Woodland Avenues)

Lecture Room

(Capacity, 250)

(From central city take Trolley Car No. 13 or 42 west on Walnut St. to 39th and Spruce Sts. Hospital is one block south on 39th St. Hospital is 5 minutes walking distance from Convention Hall.)

RALPH M. MYERSON, Presiding

9:00– 9:30 Etiology and Therapy of Hemochromatosis.
GEORGE LUDWIG and RALPH M. MYERSON.

9:30–10:00 Reactivation of Rheumatic Fever Following Mitral Commissurotomy.
BERNARD H. PASTOR.

10:00–10:15 INTERMISSION—Coffee.

10:15–10:35 Lung Biopsy in Disseminated Pulmonary Disease.
ANTHONY L. PIETROLUONGO.

10:35–11:00 Correctible Vascular Anomalies of the Kidney, Demonstrated by Aortography.
MARY S. FISHER.

P WOMAN'S MEDICAL COLLEGE OF PENNSYLVANIA

Clinics to be held at Philadelphia General Hospital

(34th Street below Spruce)

Surgical Amphitheater

(Capacity, 225)

WILLIAM G. LEAMAN, Presiding

9:00– 9:50 Surgery of the Cardiovascular System:
Surgical Aspects—THOMAS J. E. O'NEILL.
Pre- and Post-Medical Evaluation—WILLIAM G. LEAMAN.

9:50–10:00 Questions and Answers.
Examination of Patients.

10:00–10:10 INTERMISSION.

10:10–11:00 The Cardiac Clinico-Pathological Conference.
Experiences at the Massachusetts General Hospital.
HOWARD B. SPRAGUE, Boston.